National Library of Medicine - Medical Subject Headings

2002 MeSH

MeSH Descriptor Data

Return to Entry Page

MeSH Heading	Glucosylceramidase
Tree Number	D08.586.277.450.420.475.400
Annotation	/ defic: consider also GAUCHER DISEASE
Scope Note	A glycosidase that hydrolyzes a glucosylceramide to yield free ceramide plus glucose. Deficiency of this enzyme leads to abnormally high concentrations of glucosylceramide in the brain in GAUCHER DISEASE. EC 3.2.1.45.
Entry Term	Glucocerebrosidase
Entry Term	Acid beta-Glucosidase
Entry Term	Glucocerebroside beta-Glucosidase
Entry Term	Glucosyl Ceramidase
Entry Term	Glucosylceramide beta-Glucosidase
Entry Term	Glucosylsphingosine Glucosyl Hydrolase
Entry Term	beta-Glucocerebrosidase
See Also	Gaucher Disease
Allowable Qualifiers	AD AE AI AN BI BL CF CH CL CS CT DE DF DU EC GE HI IM IP ME PD PH PK PO RE SD SE ST TO TU UL UR
CAS Type 1 Name	D-Glucosyl-N-acylsphingosine glucosylhydrolase
Registry Number	EC 3.2.1.45
Previous Indexing	Cerebrosides (1970-1974)
Previous Indexing	Glucose (1970-1974)
Previous Indexing	Glycoside Hydrolases (1970-1974)
History Note	91(75); was see under GLUCOSIDASES 1975-90
Unique ID	D005962

MeSH Tree Structures

Enzymes, Coenzymes, and Enzyme Inhibitors [D08]
- Enzymes [D08.586]
  - Hydrolases [D08.586.277]
    - Glycoside Hydrolases [D08.586.277.450]
      - Glucosidases [D08.586.277.450.420]
        - Glycosylceramidase [D08.586.277.450.420.475]
          - ▶ Glucosylceramidase [D08.586.277.450.420.475.400]

National Library of Medicine - Medical Subject Headings

2002 MeSH

MeSH Descriptor Data

Return to Entry Page

MeSH Heading	1-Deoxynojirimycin
Tree Number	D03.383.621.180
Scope Note	An alpha-glucosidase inhibitor with antiviral action. Derivatives of deoxynojirimycin may have anti-HIV activity.
Entry Term	1,5-Deoxy-1,5-imino-D-mannitol
Entry Term	1-Deoxymannojirimycin
Entry Term	1,5-Dideoxy-1,5-imino-D-mannitol
Entry Term	1-Deoxynojirimycin Hydrochloride
Entry Term	Bay n 5595
Entry Term	Moranoline
Allowable Qualifiers	AA AD AE AG AI AN BL CF CH CL CS CT DU EC HI IM IP ME PD PK PO RE SD ST TO TU UR
Entry Version	DEOXYNOJIRIMYCIN
Pharm. Action	Antiviral Agents
Pharm. Action	Enzyme Inhibitors
CAS Type 1 Name	3,4,5-Piperidinetriol, 2-(hydroxymethyl)-, (2R-(2alpha,3beta,4alpha,5beta))-
Registry Number	19130-96-2
Related Number	73285-50-4 (HCl)
Related Number	84444-90-6 (1,5-dideoxy-1,5-imino-D-mannitol)
Previous Indexing	Glucosamine/analogs & derivatives (1981-1992)
Online Note	use 1-DEOXYNOJIRIMYCIN (NM) to search 1,5-DIDEOXY-1,5-IMINO-D-MANNITOL 1984-92 & DEOXYNOJIRIMYCIN 1981-92
History Note	93; was DEOXYNOJIRIMYCIN (NM) 1981-92; 1,5-DIDEOXY-1,5-IMINO-D-MANNITOL was NM 1984-92
Unique ID	D017485

MeSH Tree Structures

```
=> fil reg; d ide l10
FILE 'REGISTRY' ENTERED AT 12:48:48 ON 15 OCT 2002
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DICTIONARY FILE UPDATES:  14 OCT 2002  HIGHEST RN 461382-59-2

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PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf



L10  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   37228-64-1  REGISTRY
CN   Ceramidase, glucosyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   .beta.-D-Glucocerebrosidase
CN   .beta.-Glucocerebrosidase
CN   .beta.-Glucosylceramidase
CN   Acid .beta.-glucosidase
CN   Ceramide glucosidase
CN   Cerebroside .beta.-glucosidase
CN   E.C. 3.2.1.45
CN   Glucocerebrosidase
CN   Glucocerebroside .beta.-glucosidase
CN   Glucose cerebrosidase
CN   Glucosylceramidase
CN   Glucosylceramide .beta.-glucosidase
CN   Glucosylcerebrosidase
CN   Glucosylsphingosine .beta.-D-glucosidase
CN   Glucosylsphingosine .beta.-glucosidase
MF   Unspecified
CI   MAN
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
       CA, CAPLUS, CBNB, CEN, CIN, DDFU, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE,
       IPA, PHAR, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
             698 REFERENCES IN FILE CA (1962 TO DATE)
              12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             698 REFERENCES IN FILE CAPLUS (1962 TO DATE)
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=> fil reg; d stat que l9
FILE 'REGISTRY' ENTERED AT 13:34:41 ON 15 OCT 2002
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STRUCTURE FILE UPDATES:   14 OCT 2002  HIGHEST RN 461382-59-2
DICTIONARY FILE UPDATES:  14 OCT 2002  HIGHEST RN 461382-59-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L7                STR
```

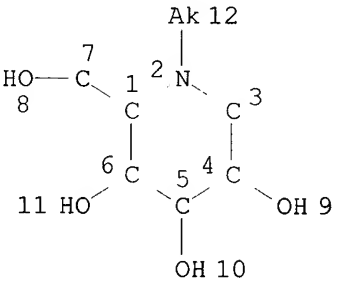

full file search done on this structure (N-alkyl derivs of deoxynojirimycin)

```
NODE ATTRIBUTES:
CONNECT IS E1  RC AT  12
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  12

STEREO ATTRIBUTES: NONE
L9          152 SEA FILE=REGISTRY SSS FUL L7

100.0% PROCESSED   8308 ITERATIONS                    152 ANSWERS
SEARCH TIME: 00.00.03
```

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=> fil medl
FILE 'MEDLINE' ENTERED AT 13:35:02 ON 15 OCT 2002

 FILE LAST UPDATED: 12 OCT 2002 (20021012/UP). FILE COVERS 1958 TO DATE.

 On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.


=> d que nos l17
L7              STR
L9          152 SEA FILE=REGISTRY SSS FUL L7
L11         408 SEA FILE=MEDLINE ABB=ON  1-DEOXYNOJIRIMYCIN/CT
L15         101 SEA FILE=MEDLINE ABB=ON  L9
L16          16 SEA FILE=MEDLINE ABB=ON  L15 NOT L11
L17          15 SEA FILE=MEDLINE ABB=ON  L16 AND (PD OR TU)/CT
```

uses of DNJ deriv.

Subheadings
PD- pharmacology
TU- therapeutic use

```
=> d ibib ab l17 1-15

L17  ANSWER 1 OF 15     MEDLINE
ACCESSION NUMBER:    92359929     MEDLINE
DOCUMENT NUMBER:     92359929   PubMed ID: 1497606
TITLE:               Activation of lipoprotein lipase in cardiac myocytes by
                     glycosylation requires trimming of glucose residues in the
                     endoplasmic reticulum.
AUTHOR:              Carroll R; Ben-Zeev O; Doolittle M H; Severson D L
CORPORATE SOURCE:    MRC Signal Transduction Group, Faculty of Medicine,
                     University of Calgary, Alberta, Canada.
CONTRACT NUMBER:     HL-21006 (NHLBI)
     HL-28481 (NHLBI)
SOURCE:              BIOCHEMICAL JOURNAL, (1992 Aug 1) 285 ( Pt 3) 693-6.
                     Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199209
ENTRY DATE:          Entered STN: 19920925
                     Last Updated on STN: 19970203
                     Entered Medline: 19920910
AB   Incubation of cycloheximide-treated cardiac myocytes results in a
     time-dependent increase in cellular and heparin-releasable lipoprotein
     lipase (LPL) activities. N-Methyldeoxynojirimycin (1 mM) and
     castanospermine (100 micrograms/ml), inhibitors of glucosidases in the
     endoplasmic reticulum (ER), prevented the increase in cellular LPL
     activity. The glucosidase inhibitors did not influence the synthesis or
     turnover of LPL protein. Therefore activation of LPL by glycosylation in
     cardiac myocytes requires the trimming of glucose residues in
     oligosaccharide chains by glucosidases of the ER.

L17  ANSWER 2 OF 15     MEDLINE
ACCESSION NUMBER:    92303625     MEDLINE
DOCUMENT NUMBER:     92303625   PubMed ID: 1609840
TITLE:               Evidence for processing of dolichol-linked oligosaccharides
                     in patients with neuronal ceroid-lipofuscinosis.
AUTHOR:              Daniel P F; Sauls D L; Boustany R M
```

CORPORATE SOURCE: Department of Biochemistry, E. K. Shriver Center, Waltham, MA 02254.
CONTRACT NUMBER: NS 24279 (NINDS)
SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (1992 Feb 15) 42 (4) 586-92.
Journal code: 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920731
Last Updated on STN: 19920731
Entered Medline: 19920722

AB In agreement with reports from other laboratories, we have shown that patients with the juvenile or late infantile forms of neuronal ceroid-lipofuscinosis (NCL) have greatly increased levels (5-fold to 20-fold) of dolichyl pyrophosphoryl oligosaccharides in their cerebral gray matter. Oligosaccharides containing 2 GlcNAc residues and 3 to 9 mannose residues were liberated by mild acid hydrolysis. The oligosaccharide profile given by brain tissue from 2 patients with infantile NCL was markedly different from that of late infantile and juvenile NCL brain, with Man9GlcNAc2 as the most abundant component and decreasing amounts of Man8- Man7- and Man6GlcNAc2. By contrast, Man5GlcNAc2 was the most abundant oligosaccharide present in all juvenile NCL brain samples analyzed. Both the susceptibility of the isolated Man5GlcNAc2 to endoglucosaminidase H digestion and permethylation analysis clearly indicated that it is not an intermediate in the biosynthesis of Glc3Man9GlcNAc2-PP-dolichol but has undergone catabolism, probably either in the endoplasmic reticulum or in the Golgi apparatus. Treatment of cultured skin fibroblasts for 7 days with N-methyldeoxynojirimycin, a potent inhibitor of the endoplasmic reticulum processing enzymes glucosidase I and II, resulted in an accumulation of the same Man5GlcNAc2-PP-dolichol species that was elevated in juvenile NCL brain. The level in untreated fibroblasts was undetectable, suggesting that inhibition of processing glucosidases has interfered with the regulation and compartmentalization of lipid-linked oligosaccharides.

L17 ANSWER 3 OF 15 MEDLINE
ACCESSION NUMBER: 91371598 MEDLINE
DOCUMENT NUMBER: 91371598 PubMed ID: 1893562
TITLE: Expression of choline acetyltransferase activity in a co-culture of spinal cord and skeletal muscle cells is inhibited by myogenic differentiation inhibitors.
AUTHOR: Kengaku M; Kawashima S; Nakane M
CORPORATE SOURCE: Department of Molecular Neurobiology, Tokyo Metropolitan Institute for Neurosciences, Japan.
SOURCE: BRAIN RESEARCH. DEVELOPMENTAL BRAIN RESEARCH, (1991 Jun 21) 60 (2) 133-6.
Journal code: 8908639. ISSN: 0165-3806.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911108
Last Updated on STN: 19980206
Entered Medline: 19911021

AB The effect of myogenic differentiation on the expression of choline acetyltransferase (ChAT) activity in co-cultured spinal cord neurons was studied. ChAT activity in spinal cord cells dissociated from 14-day mouse embryos was markedly increased when co-cultured with skeletal myotubes from 20-day embryos. This enhancement of ChAT activity was not observed in

the presence of concanavalin A (ConA) or N-methyl-1-deoxynojirimycin (MDJN) which inhibits myoblast fusion, creatine phosphokinase and acetylcholinesterase activities in muscle cells. ChAT activity in spinal cord neurons cultured alone was unaffected by these agents. The inhibitory effect of ConA and MDJN was reversible, with an almost full recovery of ChAT activity following removal of the agents. Addition of ConA or MDJN after myotube formation exerted little inhibitory effect on ChAT activity. The effects of ConA and MDJN on ChAT activity in co-cultures were comparable to those on creatine phosphokinase and acetylcholinesterase. These observations indicate that the neurotrophic effects of skeletal muscle cells on spinal cord neurons are dependent on the differentiation state of the muscle cells.

L17 ANSWER 4 OF 15 MEDLINE
ACCESSION NUMBER: 91312437 MEDLINE
DOCUMENT NUMBER: 91312437 PubMed ID: 1857411
TITLE: Anti-HIV drug mechanism.
AUTHOR: Jones I M; Jacob G S
SOURCE: NATURE, (1991 Jul 18) 352 (6332) 198.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910913
Last Updated on STN: 19970203
Entered Medline: 19910828

L17 ANSWER 5 OF 15 MEDLINE
ACCESSION NUMBER: 91134980 MEDLINE
DOCUMENT NUMBER: 91134980 PubMed ID: 1704656
TITLE: Inhibition of HIV and SIV infectivity by blockade of alpha-glucosidase activity.
AUTHOR: Ratner L; vander Heyden N; Dedera D
CORPORATE SOURCE: Department of Medicine, Washington University, St. Louis, Missouri 63110.
CONTRACT NUMBER: AI24745 (NIAID)
AI25903 (NIAID)
AI27302 (NIAID)
SOURCE: VIROLOGY, (1991 Mar) 181 (1) 180-92.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910405
Last Updated on STN: 19970203
Entered Medline: 19910315

AB Processing of HIV and SIV envelope oligosaccharides is critical for proper intracellular trafficking and function. An inhibitor of alpha-glucosidases I and II, N-butyl deoxynojirimycin (N-BuDNJ), retards HIV-1 and SIVmac spread in lymphocytes and monocytes by diminishing virus infectivity, and also causes a reduction in syncytia formation between infected cells and uninfected lymphocytes. N-BuDNJ retards envelope processing from the precursor form to the mature surface (SU) and transmembrane proteins in HIV-1- and SIVmac-infected cells, as well as in cells infected with vaccinia-HIV-1 envelope recombinant virus. However, no significant reduction is seen in the amount of SU in released virus particles, though the virus particle-associated SU from N-BuDNJ-treated cells has an altered electrophoretic mobility. In contrast, N-BuDNJ had no effect on GAG protein synthesis and processing. These findings demonstrate a critical

requirement for oligosaccharide processing by alpha-glucosidases I and II for HIV-1 and SIVmac envelope processing and fusogenicity.

L17 ANSWER 6 OF 15 MEDLINE
ACCESSION NUMBER: 90359716 MEDLINE
DOCUMENT NUMBER: 90359716 PubMed ID: 2561901
TITLE: Several new AIDS drugs being tested.
AUTHOR: Anonymous
SOURCE: ONCOLOGY, (1989 Jun) 3 (6) 114, 120.
Journal code: 8712059. ISSN: 0890-9091.
PUB. COUNTRY: United States
DOCUMENT TYPE: News Announcement
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901109
Last Updated on STN: 19980206
Entered Medline: 19901004

L17 ANSWER 7 OF 15 MEDLINE
ACCESSION NUMBER: 90303970 MEDLINE
DOCUMENT NUMBER: 90303970 PubMed ID: 2364019
TITLE: Attenuation of HIV-1 infectivity by an inhibitor of oligosaccharide processing.
AUTHOR: Dedera D; Vander Heyden N; Ratner L
CORPORATE SOURCE: Department of Medicine, Washington University, St. Louis, Missouri 63110.
SOURCE: AIDS RESEARCH AND HUMAN RETROVIRUSES, (1990 Jun) 6 (6) 785-94.
Journal code: 8709376. ISSN: 0889-2229.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900921
Last Updated on STN: 19970203
Entered Medline: 19900813

AB A series of inhibitors of trimming glucosidases and mannosidases were examined for antiviral activity toward HIV-1. N-butyl deoxynojirimycin (N-buDNJ) was found to be the most potent agent studied. Treatment of acutely infected lymphoid cells with 2.0 mM N-buDNJ reduced virus yield more than 90%, without affecting cell growth. Though lower concentrations of N-buDNJ (0.002-0.2 mM) did not affect HIV-1 production, there was complete inhibition of syncytia formation. Treatment of chronically infected lymphoid cells with 0.1-1.0 mM N-buDNJ resulted in no significant change in virus production, but 80% reduction of infectivity. The attenuation in HIV-1 infectivity was due at least partially to diminished binding to CD4+ lymphoid cells. Chronically infected lymphoid cells treated with 0.02-1.0 mM N-buDNJ for at least 3 days were markedly impaired in their ability to form syncytia with uninfected lymphoid cells. N-buDNJ treatment of HIV-1 infected cells resulted in both a reduction in the cell surface envelope proteins, and an increase in their apparent molecular weight. These results show that N-buDNJ can be used to impair the infectivity of HIV-1 without significant toxicity.

L17 ANSWER 8 OF 15 MEDLINE
ACCESSION NUMBER: 90266453 MEDLINE
DOCUMENT NUMBER: 90266453 PubMed ID: 1693245
TITLE: The significance of carbohydrate trimming for the antigenicity of the Semliki Forest virus glycoprotein E2.
AUTHOR: Kaluza G; Repges S; McDowell W
CORPORATE SOURCE: Institut fur Virologie, Justus Leibig Universitat Giessen,

Federal Republic of Germany.
SOURCE: VIROLOGY, (1990 Jun) 176 (2) 369-78.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 19900810
Last Updated on STN: 19990129
Entered Medline: 19900705

AB Six groups, designated a-f, of noncompeting murine monoclonal antibodies to the envelope glycoprotein E2 of Semliki Forest virus (SFV) have been used to analyze antigenic changes caused by differences in the carbohydrate chain composition of the envelope glycoprotein E2 in the virion. Deletion of terminal sialic acids as observed in virus progeny from mosquito cells did not affect antigenic properties. Inhibition of the trimming pathway in infected chicken cells by the mannosidase I inhibitor dMM led to infectious virus particles containing mannose-rich oligosaccharides of the composition Man9(GlcNAc)2 in the envelope glycoproteins. This alteration had no effect on antigenicity. If inhibition was, however, performed with MdN which acts on alpha-glucosidase giving rise to virions with glycoproteins containing three additional glucose residues in the carbohydrate chains [Glc3Man7,8,9(GlcNAc)2], significant antigenic changes were observed. The six epitopes were differently affected by the underlying structural change and the pattern of exposition of epitopes was not identical with that observed after cleavage of intramolecular disulfide bonds. Concomitantly, the cleavage rate of gp62, the intracellular precursor molecule of the glycoproteins E2 and E3 of the virus particle, was reduced causing a reduction of virus yield. It is concluded that the existence of untrimmed carbohydrate chains is sufficient to allow SFV maturation. The trimming reactions improve this process in a matter suggesting that the carbohydrate chains influence intracellular traffic (addressing) of the respective glycoprotein.

L17 ANSWER 9 OF 15 MEDLINE
ACCESSION NUMBER: 89270116 MEDLINE
DOCUMENT NUMBER: 89270116 PubMed ID: 2729046
TITLE: Experimental treatments for HIV-infected patients.
AUTHOR: Anonymous
SOURCE: AMERICAN FAMILY PHYSICIAN, (1989 Jun) 39 (6) 330.
Journal code: 1272646. ISSN: 0002-838X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890707

L17 ANSWER 10 OF 15 MEDLINE
ACCESSION NUMBER: 88013890 MEDLINE
DOCUMENT NUMBER: 88013890 PubMed ID: 3116410
TITLE: Effect of trimming inhibitors on the secretion and biological activity of a murine IgE monoclonal antibody.
AUTHOR: Granato D A; Neeser J R
CORPORATE SOURCE: Nestec Ltd., Nestle Research Centre, Lausanne, Switzerland.
SOURCE: MOLECULAR IMMUNOLOGY, (1987 Aug) 24 (8) 849-55.
Journal code: 7905289. ISSN: 0161-5890.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198711
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871109

AB Since secretion of IgE antibodies is known to be blocked by tunicamycin, the first aim of the present study was to determine at which step of glycosylation or processing secretion was restored. For this purpose, murine hybridoma cells secreting an anti beta-lactoglobulin IgE were incubated either in the presence of inhibitors of glucosidase I (castanospermine or N-methyl-1-deoxynojirimycin), or of an inhibitor of Golgi mannosidase II (swainsonine). Terminal galactoses predominate on the native IgE N-linked carbohydrate chains. The action of the trimming inhibitors, which results in changes in these terminal galactose residues, was monitored through detecting binding modifications to Concanavalin A and to the lectin of Ricinus communis. The antibody activity was also evaluated by a radioimmunoassay. It was shown that neither secretion nor anti beta-lactoglobulin activity of the IgE antibody are modified in the presence of any of the trimming inhibitors, whereas secretion is blocked in the presence of tunicamycin. Other biological activities of this IgE were investigated: no difference was observed in the binding of the carbohydrate-modified IgE molecules to normal mouse mast cells, nor to RBL-1 cells, as demonstrated by passive cutaneous anaphylaxis and in vitro binding tests respectively. However, traces of unglycosylated epsilon chain (mol. wt 61,000) found in tunicamycin treated cell supernatant did not bind to RBL-1 cell Fc epsilon receptors. These findings globally suggest that secretion occurs only if the tetradecasaccharide precursor of N-linked carbohydrate chains is transferred from its lipid-carrier to the polypeptide. Further, the presence of such non-processed oligosaccharides (Glc3Man9GlcNAc2) on IgE, does not seem to modify any of the biological activities of this molecule.

L17 ANSWER 11 OF 15 MEDLINE
ACCESSION NUMBER: 87057249 MEDLINE
DOCUMENT NUMBER: 87057249 PubMed ID: 3782099
TITLE: Transfer of nonglucosylated oligosaccharide from lipid to protein in a mammalian cell.
AUTHOR: Romero P A; Herscovics A
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1986 Dec 5) 261 (34) 15936-40.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19870107

AB We have previously shown that the glucosidase inhibitor, N-methyl-1-deoxynojirimycin (MedJN), only partially inhibited N-linked complex oligosaccharide biosynthesis in F9 teratocarcinoma cells whereas the alpha-mannosidase I inhibitor, manno-1-deoxynojirimycin, completely prevented this synthesis (Romero, P. A. and Herscovics, A. (1986) Carbohydr. Res. 151, 21-28). In order to determine whether a pathway independent of processing glucosidases can occur, F9 cells were pulse-labeled for 2 min with D-[2-3H]mannose in the presence or absence of 2 mM MedJN. In control cells, Man7GlcNAc was identified in the protein-bound oligosaccharides released with endo-beta-N-acetylglucosaminidase H, in addition to the expected Glc1-3Man9GlcNAc and Man9GlcNAc arising from processing of Glc3Man9GlcNAc. MedJN completely prevented the removal of glucose residues from Glc3Man9GlcNAc, but did not

greatly affect the appearance of Man7GlcNAc associated with protein. Labeled Man7GlcNAc was also found in the lipid-linked oligosaccharides of both control and treated cells. The 2-min pulse-labeled Man7GlcNAc obtained from both the lipid and protein fractions were shown to have identical structures by concanavalin A-Sepharose chromatography and by acetolysis and were clearly different from the Man7GlcNAc obtained from the usual processing pathway. These results demonstrate that transfer of a nonglucosylated oligosaccharide (Man7GlcNAc2) from dolichyl pyrophosphate to protein occurs in F9 cells.

L17 ANSWER 12 OF 15 MEDLINE
ACCESSION NUMBER: 86310826 MEDLINE
DOCUMENT NUMBER: 86310826 PubMed ID: 3018522
TITLE: Transformation by the v-fms oncogene product: role of glycosylational processing and cell surface expression.
AUTHOR: Nichols E J; Manger R; Hakomori S; Herscovics A; Rohrschneider L R
CONTRACT NUMBER: CA20551 (NCI)
CA28151 (NCI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1985 Dec) 5 (12) 3467-75.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198610
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19861003

AB The effect of glycosylational-processing inhibitors on the synthesis, cell surface expression, endocytosis, and transforming function of the v-fms oncogene protein (gp140fms) was examined in McDonough feline sarcoma virus-transformed Fischer rat embryo (SM-FRE) cells. Swainsonine (SW), a mannosidase II inhibitor, blocked complete processing, but an abnormal v-fms protein containing hybrid carbohydrate structures was expressed on the cell surface. SW-treated SM-FRE cells retained the transformed phenotype. In contrast, two glucosidase I inhibitors (castanospermine [CA] and N-methyl-1-deoxynojirimycin [MdN]) blocked carbohydrate remodeling at an early stage within the endoplasmic reticulum and prevented cell surface expression of v-fms proteins. CA-treated SM-FRE cells reverted to the normal phenotype. Neither SW, CA, nor MdN affected either endocytosis or the tyrosine kinase activity associated with the v-fms gene product in vitro. These results demonstrate the necessity of carbohydrate processing for cell surface expression of the v-fms gene product and illustrate the unique ability to modulate the transformed state of SM-FRE cells with the glycosylational-processing inhibitors CA and MdN.

L17 ANSWER 13 OF 15 MEDLINE
ACCESSION NUMBER: 84123045 MEDLINE
DOCUMENT NUMBER: 84123045 PubMed ID: 6320537
TITLE: Processing of gPr92env, the precursor to the glycoproteins of Rous sarcoma virus: use of inhibitors of oligosaccharide trimming and glycoprotein transport.
AUTHOR: Bosch J V; Schwarz R T
SOURCE: VIROLOGY, (1984 Jan 15) 132 (1) 95-109.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198403
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203

Entered Medline: 19840322

AB A number of aspects of the processing of gPr92env, the precursor to the viral glycoproteins gp85 and gp35 of Rous sarcoma virus (RSV), have been studied. First, the kinetics of gPr92env processing have been examined, revealing that the precursor is overproduced in the infected cell and only a small percentage (less than 5%) is converted into mature glycoprotein in virus particles. Second, the effects of inhibitors of intracellular transport (monensin) and oligosaccharide trimming (N-methyl-1-deoxynojirimycin (MdN) and bromoconduritol (BC)) on the processing of gPr92env have been examined. It could be shown with all three inhibitors that proteolytic cleavage of gPr92env could occur although oligosaccharide trimming was inhibited. The aberrant cleavage products, gp75mon and gp30mon, produced in the presence of monensin, carry oligosaccharides where only 1-3 mannose residues have been removed in comparison to the precursor gPr92env (this latter carries predominantly Man9(GlcNAc)2). Virus particles containing the aberrant glycoproteins were released in virtually normal amounts and were infectious. In the presence of MdN and BC, viral glycoprotein precursors carrying three (MdN) or one (BC) glucose on the high-mannose oligosaccharide could be detected intracellularly. The aberrant precursors could be proteolytically cleaved to gp80MdN and gp75BC which are equivalent to gp85 but carry the smaller glucose-containing high-mannose oligosaccharides instead of the large, complex, sialidated oligosaccharides of mature glycoprotein. In the presence of MdN, the abnormal glycoproteins were incorporated into virions which were fully infectious.

L17 ANSWER 14 OF 15 MEDLINE
ACCESSION NUMBER: 84123036 MEDLINE
DOCUMENT NUMBER: 84123036 PubMed ID: 6695499
TITLE: Effect of inhibitors of glycosylation on proteolytic activation of avian influenza virus hemagglutinins: discrimination between tryptic cleavage and elimination of the connecting peptide.
AUTHOR: Bosch F X; Orlich M; Legler G; Schwarz R T; Rott R
SOURCE: VIROLOGY, (1984 Jan 15) 132 (1) 199-204.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198403
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840322

AB The glycosylation inhibitors tunicamycin (TM), 2-deoxyglucose (2-dg), bromoconduritol (BC; 3,5/4,6-6-bromo 3,4,5-trihydroxycyclohex-1-ene), and N-methyl-deoxynojirimycin (MdN) have been used to study the role of glycosylation in the two proteolytic reactions involved in the biological activation of H7 influenza virus hemagglutinins (HAs): trypsinlike cleavage and subsequent elimination of the connecting peptide. The results obtained revealed that trypsin-like cleavage of the HAs of pathogenic strains does not require glycosylation, since these HAs were efficiently cleaved in the presence of TM and 2-dg. The elimination of the connecting peptide between HA1 and HA2, however, appears to require the transfer of oligosaccharides onto the HA polypeptide, since this activity was blocked by TM and by 2-dg. Elimination was not blocked by BC or MdN, which inhibit glucose trimming and subsequent conversion of the high-mannose type to the complex type of carbohydrate.

L17 ANSWER 15 OF 15 MEDLINE
ACCESSION NUMBER: 84046704 MEDLINE
DOCUMENT NUMBER: 84046704 PubMed ID: 6636538
TITLE: N-methyl-1-deoxynojirimycin, a novel inhibitor of

glycoprotein processing, and its effect on fowl plague virus maturation.

AUTHOR: Romero P A; Datema R; Schwarz R T

SOURCE: VIROLOGY, (1983 Oct 15) 130 (1) 238-42.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198312
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19831217

AB The glucose analogue N-methyl-1-deoxynojirimycin was found to be a specific inhibitor of the trimming of the outermost glucose residue of the N-linked precursor-oligosaccharide Glc3Man9GlcNAc2, and therefore of oligosaccharide processing, in fowl plague virus-infected chicken-embryo cells. The fowl plague virus glycoproteins in N-methyl-1-deoxynojirimycin-treated cells contain oligosaccharides of the composition Glc3ManxGlcNAc2 (x = 7, 8, and 9). Inhibition of trimming of the outermost glucose residues does not prevent release of infectious virus with oligosaccharides of the composition Glc3Man7(GlcNAc)2. On the other hand inhibition of the trimming of the innermost glucose residue does inhibit release of infectious virus (Datema, R., Romero, P. A., Legler , G., and Schwarz, R. T. Proc. Nat. Acad. Sci. USA 79, 6787-6791 (1982)).

```
=> d que l27
L18          856 SEA FILE=MEDLINE ABB=ON  GLUCOSYLCERAMIDASE/CT
L22         2280 SEA FILE=MEDLINE ABB=ON  GAUCHER DISEASE/CT
L26          264 SEA FILE=MEDLINE ABB=ON  L18(L)(TU OR PD OR PK OR AD)/CT
L27            9 SEA FILE=MEDLINE ABB=ON  L26 NOT L22
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Subheadings
TU - therapeutic use
PD - pharmacology
PK - pharmacokinetics
AD - administration & dosage

uses of glucocerebrosidase other than to treat Gaucher's disease

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=> d ibib ab l27 1-9

L27  ANSWER 1 OF 9     MEDLINE
ACCESSION NUMBER:    2001228162     MEDLINE
DOCUMENT NUMBER:     21164782   PubMed ID: 11264150
TITLE:               Plasma glucosylceramide deficiency as potential risk factor
                     for venous thrombosis and modulator of anticoagulant
                     protein C pathway.
COMMENT:             Comment in: Blood. 2001 Apr 1;97(7):1905
AUTHOR:              Deguchi H; Fernandez J A; Pabinger I; Heit J A; Griffin J H
CORPORATE SOURCE:    Department of Molecular and Experimental Medicine, The
                     Scripps Research Institute, La Jolla, CA 92037, USA.
CONTRACT NUMBER:     R37HL52246 (NHLBI)
     RO1HL21544 (NHLBI)
SOURCE:              BLOOD, (2001 Apr 1) 97 (7) 1907-14.
                     Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200104
ENTRY DATE:          Entered STN: 20010502
                     Last Updated on STN: 20010502
                     Entered Medline: 20010426
AB   To assess the relationship between venous thrombosis and plasma
     glucosylceramide (GlcCer) or phosphatidylethanolamine (PE), plasma levels
     of GlcCer and PE were determined for 70 venous thrombosis patients
     referred for evaluation and 70 healthy blood donors. The mean GlcCer
     level, but not the PE level, was lower in patients versus controls (4.9 vs
     6.5 microg/mL [P =.0007] and 66 vs 71 microg/mL [P =.48], respectively).
     As a measure of relative risk, the odds ratio for deep vein thrombosis in
     subjects with GlcCer levels below the 10th percentile of controls was 5.7
     (95% CI, 2.3-14). To assess the influence of glycolipids on anticoagulant
     response to activated protein C (APC):protein S in modified prothrombin
     time assays, the effects of depleting endogenous plasma GlcCer by
     glucocerebrosidase treatment or of adding exogenous purified GlcCer or
     other neutral glycolipids to plasma were tested. Glucocerebrosidase
     treatment reduced plasma sensitivity to APC:protein S in parallel with
     GlcCer reduction. Exogenously added GlcCer and the homologous
     Glc-containing globotriaosylceramide (Gb3Cer), but not galactosylceramide,
     dose-dependently prolonged clotting times of normal plasma in the
     presence, but not absence, of APC:protein S, which suggests that GlcCer or
     Gb3Cer can enhance protein C pathway anticoagulant activity. In studies
     using purified proteins, inactivation of factor Va by APC:protein S was
     enhanced by GlcCer alone and by GlcCer in multicomponent vesicles
     containing phosphatidylserine and phosphatidylcholine. These results
     suggest that the neutral glycolipids GlcCer and Gb3Cer may directly
     contribute to the anticoagulant activity of the protein C pathway and that
     deficiency of plasma GlcCer may be a risk factor for venous thrombosis.
     (Blood. 2001;97:1907-1914)

L27  ANSWER 2 OF 9     MEDLINE
ACCESSION NUMBER:    2000031171     MEDLINE
DOCUMENT NUMBER:     20031171   PubMed ID: 10566895
TITLE:               Prophylaxis of antibody-induced acute glomerulonephritis
```

with genetically modified bone marrow-derived vehicle cells.

AUTHOR: Yokoo T; Ohashi T; Utsunomiya Y; Kojima H; Imasawa T; Kogure T; Hisada Y; Okabe M; Eto Y; Kawamura T; Hosoya T

CORPORATE SOURCE: Department of Internal Medicine (II), Jikei University School of Medicine, Tokyo, Japan.. tyokoo@jikei.ac.jp

SOURCE: HUMAN GENE THERAPY, (1999 Nov 1) 10 (16) 2673-8. Journal code: 9008950. ISSN: 1043-0342.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199912

ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991216

AB Glomerulonephritis is an inflammatory disease of the renal glomerulus, which often progresses either slowly or rapidly, ending in renal death despite the availability of various antiinflammatory drugs. Gene therapy may be a promising method of suppressing the progression of glomerulonephritis through the blockage of key inflammatory molecule(s). However, the difficulty of local gene delivery into the glomerulus has made the clinical use of gene therapy difficult. As a solution to this issue, we applied a novel ex vivo technique that may allow site-specific gene delivery into the inflamed site and thus suppress local inflammation in the glomerulus, and examined the feasibility of this system as a prophylaxis of glomerulonephritis. The gene encoding the antiinflammatory cytokine interleukin 1 receptor antagonist (IL-1ra) was delivered into animal models of inflamed glomeruli evoked by anti-glomerular basement membrane antibody; this animal model is an analog of the human Goodpasture syndrome. Vehicle cells did indeed accumulate in the glomeruli on the induction of nephritis and were confirmed to secrete recombinant IL-1ra. Renal functions as well as morphology were preserved by this intervention for up to 14 days after IL-1ra introduction. These data demonstrate the possible application of gene therapy for acute glomerulonephritis. A gene encoding an antiinflammatory molecule, IL-1 receptor antagonist, was delivered into inflamed glomeruli, using a technique that may allow site-specific gene delivery into inflamed tissues. The progression of experimental acute glomerulonephritis was effectively suppressed by this intervention for at least 14 days after gene introduction. This success may strengthen the rationale for gene therapy in the treatment of inflammatory diseases such as glomerulonephritis.

L27 ANSWER 3 OF 9 MEDLINE

ACCESSION NUMBER: 1999045001 MEDLINE

DOCUMENT NUMBER: 99045001 PubMed ID: 9829536

TITLE: Long-term expression, systemic delivery, and macrophage uptake of recombinant human glucocerebrosidase in mice transplanted with genetically modified primary myoblasts.

AUTHOR: Liu C; Dunigan J T; Watkins S C; Bahnson A B; Barranger J A

CORPORATE SOURCE: Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, PA 15261, USA.

CONTRACT NUMBER: DK 43709 (NIDDK)

SOURCE: HUMAN GENE THERAPY, (1998 Nov 1) 9 (16) 2375-84. Journal code: 9008950. ISSN: 1043-0342.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199901

ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990114

AB A critical requirement for treatment of Gaucher disease via systemic delivery of recombinant GC is that secreted enzyme be in a form available for specific takeup by macrophages in vivo. In this article we investigated if transplanted primary myoblasts can sustain expression of human GC in vivo and if the secreted transgene product is taken up by macrophages. Transduced primary murine myoblasts were implanted into syngeneic C3H/HeJ mice. The results demonstrated that transplanted mice sustained long-term expression of transferred human GC gene in vivo. Furthermore, human GC is secreted into the circulation of mice transplanted with syngeneic primary myoblasts retrovirally transduced with human GC cDNA. The transplanted primary myoblasts differentiate and fuse with adjacent mature myofibers, and express the transgene product for up to 300 days. Human GC in the circulation reaches levels of 20-280 units/ml of plasma. Immunohistochemical studies of the target organs revealed that the secreted human GC is taken up by macrophages in liver and bone marrow. Immunochemical identification of reisolated myoblasts from transplanted mice showed that MFG-GC-transduced cells also survived as muscle stem cells in the implanted muscle. These results present in encouraging prospect for the treatment of Gaucher disease.

L27 ANSWER 4 OF 9 MEDLINE
ACCESSION NUMBER: 96124641 MEDLINE
DOCUMENT NUMBER: 96124641 PubMed ID: 8577062
TITLE: Enzyme replacement therapy of patients with lysosomal storage disease.
AUTHOR: Takada G; Takahashi T
CORPORATE SOURCE: Akita University School of Medicine, Department of Pediatrics.
SOURCE: NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1995 Dec) 53 (12) 3077-82. Ref: 22
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960321
Last Updated on STN: 19960321
Entered Medline: 19960312

AB The history and bases of enzyme replacement therapy are briefly reviewed. The enzyme replacement therapy for Gaucher disease type 1, which has been developed for clinical use and is about to be introduced in our country, was described somewhat in detail under the items of the modification of human placental glucocerebrosidase into the macrophage-terminated enzyme, its clinical usage, effects and their evaluations, adverse effects, and new attempts of its application for Gaucher disease types II and III, now being under clinical trials. Also touched are developments of other enzymes for such lysosomal diseases as Fabry disease, Pompe disease, Hurler syndrome, Hunter disease, and Sly disease.

L27 ANSWER 5 OF 9 MEDLINE
ACCESSION NUMBER: 96031106 MEDLINE
DOCUMENT NUMBER: 96031106 PubMed ID: 8550385
TITLE: A biochemical and immunocytochemical study on the targeting of alglucerase in murine liver.
AUTHOR: Willemsen R; Tibbe J J; Kroos M A; Martin B M; Reuser A J; Ginns E I
CORPORATE SOURCE: Department of Clinical Genetics, Erasmus University, Rotterdam, The Netherlands.
SOURCE: HISTOCHEMICAL JOURNAL, (1995 Aug) 27 (8) 639-46.
Journal code: 0163161. ISSN: 0018-2214.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960306
Last Updated on STN: 19960306
Entered Medline: 19960222

AB A current hypothesis is that functional glucocerebrosidase needs to be delivered to the lysosomes of tissue macrophages to guarantee successful enzyme therapy for Gaucher's disease. In this study, biochemical and immunohistochemical techniques were applied to identify in mice the localization of intravenously administered alglucerase (human modified placental glucocerebrosidase). Only in liver and spleen was a significant increase of glucocerebrosidase activity observed, with a maximum level at 15 minutes after enzyme infusion. The uptake of enzyme by liver was sufficiently high to allow more detailed studies on the (sub)cellular distribution of human alglucerase. The enzyme in liver is localized both in the endosomal-lysosomal system of the Kupffer cells and the endothelial cells lining the lumen of the sinusoids. Uptake by both of these types of cell is prevented by mannan. The results suggest that the cellular mechanisms responsible for improvement of Gaucher patients receiving alglucerase treatment is probably more complicated than previously recognized.

L27 ANSWER 6 OF 9 MEDLINE
ACCESSION NUMBER: 95123042 MEDLINE
DOCUMENT NUMBER: 95123042 PubMed ID: 7822772
TITLE: Immunoelectron microscopic localization of mannose-terminal glucocerebrosidase in lysosomes of rat liver Kupffer cells.
AUTHOR: Murray G J; Jin F S
CORPORATE SOURCE: Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland.
SOURCE: JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (1995 Feb) 43 (2) 149-58.
Journal code: 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 19950223
Entered Medline: 19950214

AB Knowledge of the cellular distribution and subcellular localization of mannose-terminal glucocerebrosidase after intravenous infusion is necessary for understanding the efficacy of targeted enzyme replacement therapy for Gaucher's disease. Selective uptake of mannose-terminal glucocerebrosidase by Kupffer cells in rat liver has been previously demonstrated biochemically. In this study we used immunohistochemical and immunogold labeling techniques to provide direct visual proof for the localization of the delivered enzyme. Light microscopy confirmed biochemical data identifying non-parenchymal cells as the primary target of the modified glucocerebrosidase. Using a primary antibody specific for glucocerebrosidase and a secondary gold-conjugated antibody, we used immunoelectron microscopy to quantify the extent and distribution of exogenous enzyme in various cell types in rat liver and its localization within their respective subcellular organelles. Thirty minutes after intravenous administration of mannose-terminal glucocerebrosidase, enzyme was localized primarily in lysosomes of Kupffer cells. Of eight intact Kupffer cells counted, 16 of 21 lysosomes (78%) contained immunogold conjugates (average concentration 293 gold particles/micron 2). Of 589

particles counted in these lysosomes, 485 (82%) were localized within the lumen of the lysosome; only 104 (18%) were membrane-associated. Five of the 21 lysosomes counted were negative for gold. No gold particles were found in the mitochondria of Kupffer cells and very few particles (8.2/microns 2) were found over the nucleus. The density of gold particles was also low over the nucleus (7.2/microns 2), mitochondria (8.8/microns 2), and lysosomes (7.9/microns 2) of hepatocytes. No specific labeling was observed in erythrocytes, platelets, lymphocytes, pit cells, fat-storing cells, or bile duct. Background labeling of control liver sections from rats receiving saline injection was 8.2 +/- 1.4 gold particles/microns 2. We conclude that mannose-terminal glucocerebrosidase is delivered to the lysosomes of Kupffer cells in liver and that it is distributed both within the lumen (82%) and over the membrane (18%) of the lysosome, with a slight preferential association with the membrane. These findings may provide insights into the design of more effective therapeutic enzyme preparations for the treatment of Gaucher's disease.

L27 ANSWER 7 OF 9 MEDLINE
ACCESSION NUMBER: 86161718 MEDLINE
DOCUMENT NUMBER: 86161718 PubMed ID: 3913525
TITLE: Erythrocyte carriers.
AUTHOR: Ihler G M; Tsang H C
SOURCE: CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, (1985) 1 (2) 155-87. Ref: 202
Journal code: 8511159. ISSN: 0743-4863.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198605
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19980206
Entered Medline: 19860506

AB The properties of erythrocytes used as carriers for drugs, enzymes, and DNA will be reviewed. One potential application is delivery of these substances to cells responsible for or capable of erythrophagocytosis and are located primarily in the liver and the spleen. A second potential application depends on the ability of loaded cells to survive for substantial periods of time in the circulation after reinfusion. Circulating cells used as drug carriers may be able to modify the pharmacokinetics of administered drugs and if used as enzyme carriers, they may be able to alter the level of various substances in the plasma. Erythrocytes in vitro may fuse with recipient cells, introducing their contents in a functional form into recipient cells. Nucleic acids, either RNA or DNA, as well as enzymes or other entrapped substances, may be transferred in this manner.

L27 ANSWER 8 OF 9 MEDLINE
ACCESSION NUMBER: 86103228 MEDLINE
DOCUMENT NUMBER: 86103228 PubMed ID: 4084247
TITLE: Targeting of synthetically glycosylated human placental glucocerebrosidase.
AUTHOR: Murray G J; Doebber T W; Shen T Y; Wu M S; Ponpipom M M; Bugianesi R L; Brady R O; Barranger J A
SOURCE: BIOCHEMICAL MEDICINE, (1985 Oct) 34 (2) 241-6.
Journal code: 0151424. ISSN: 0006-2944.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321

Last Updated on STN: 19900321
Entered Medline: 19860218

AB Human placental beta-glucocerebrosidase modified by covalent attachment of N2-(N2, N6-bis [3-(alpha-D-mannopyranosylthio)propionyl]-L-lysyl)-N6-[3-(alpha-D-mannopyranosylthio)propionyl]-L-lysine was administered to rats by intravenous injection. Comparison of enzyme distribution in isolated liver cell populations indicates an increase in enzyme-specific activity of 18-fold in nonparenchymal cells and only 1.5-fold to hepatocytes compared to uninjected control animals. This macrophage-specific delivery of an active lysosomal enzyme has potential for application in enzyme replacement trials.

L27 ANSWER 9 OF 9 MEDLINE
ACCESSION NUMBER: 85199027 MEDLINE
DOCUMENT NUMBER: 85199027 PubMed ID: 3994697
TITLE: Lectin-specific targeting of beta-glucocerebrosidase to different liver cells via glycosylated liposomes.
AUTHOR: Das P K; Murray G J; Zirzow G C; Brady R O; Barranger J A
SOURCE: BIOCHEMICAL MEDICINE, (1985 Feb) 33 (1) 124-31.
Journal code: 0151424. ISSN: 0006-2944.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198506
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850614

AB Galactosylated and mannosylated liposomes were more efficient in transporting liposome-entrapped beta-glucocerebrosidase to liver compared to nonglycosylated liposomes. The enzyme entrapped to glycoside-bearing liposomes was found to be cleared at a much faster rate than that entrapped in liposomes having no sugar on their surface. Asialoorosomucoid and hydrolyzed mannan were found to inhibit both the clearance and the uptake of galactosylated and mannosylated liposomes, respectively, supporting involvement of lectin-sugar interaction. Further studies on the uptake of glucocerebrosidase by isolated liver cells revealed that the enzyme entrapped in mannosylated liposomes has much higher affinity for nonparenchymal cells whereas the assimilation of the entrapped enzyme into hepatocytes is clearly favored for liposomes having galactose on their surface.

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=> fil capl; d que nos 136; fil medl; d que nos 150; fil embase; d que nos 171; d que nos
166; fil wpids; d que 190
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L28         224 SEA FILE=CAPLUS ABB=ON  L9
L33         106 SEA FILE=CAPLUS ABB=ON  L28(L)(THU OR BAC OR PAC OR DMA OR
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L35         899 SEA FILE=CAPLUS ABB=ON  GAUCHER?/OBI
L36          12 SEA FILE=CAPLUS ABB=ON  L33 AND L35
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Roles THU - Therapeutic use
BAC - Biological activity
PAC - pharmacologic activity
DMA - drug mechanism of action
PKT - pharmacokinetics

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MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

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L15         101 SEA FILE=MEDLINE ABB=ON  L9
L48         424 SEA FILE=MEDLINE ABB=ON  (L11 OR L15)
L49        2280 SEA FILE=MEDLINE ABB=ON  GAUCHER DISEASE/CT
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 FILE COVERS 1974 TO 10 Oct 2002 (20021010/ED)

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 substance identification.


L7              STR
L9          152 SEA FILE=REGISTRY SSS FUL L7
L58         122 SEA FILE=EMBASE ABB=ON  L9
L61        1923 SEA FILE=EMBASE ABB=ON  GAUCHER DISEASE/CT
L65         349 SEA FILE=EMBASE ABB=ON  L61(L)DT/CT
L66          13 SEA FILE=EMBASE ABB=ON  L65 AND L58
L67          10 SEA FILE=EMBASE ABB=ON  L61/MAJ AND L58
L69           4 SEA FILE=EMBASE ABB=ON  L67 NOT L66
L70           3 SEA FILE=EMBASE ABB=ON  BIOSYNTHESIS/CT AND L67
L71           2 SEA FILE=EMBASE ABB=ON  L70 AND L69
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Subheading
DT = drug therapy

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L7              STR
L9          152 SEA FILE=REGISTRY SSS FUL L7
L58         122 SEA FILE=EMBASE ABB=ON  L9
L61        1923 SEA FILE=EMBASE ABB=ON  GAUCHER DISEASE/CT
L65         349 SEA FILE=EMBASE ABB=ON  L61(L)DT/CT
L66          13 SEA FILE=EMBASE ABB=ON  L65 AND L58


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    http://www.derwent.com/userguides/dwpi_guide.html <<<


L86          69 SEA FILE=WPIDS ABB=ON  ?DEOXYNOJIRIMYCIN?
L87         266 SEA FILE=WPIDS ABB=ON  GAUCHER?
L89          39 SEA FILE=WPIDS ABB=ON  ?DEOXY NOJIRIMYCIN?
L90           5 SEA FILE=WPIDS ABB=ON  (L89 OR L86) AND L87
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=> dup rem l50,l36,l66,l71,l90
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PROCESSING COMPLETED FOR L36
PROCESSING COMPLETED FOR L66
PROCESSING COMPLETED FOR L71
PROCESSING COMPLETED FOR L90
L99           30 DUP REM L50 L36 L66 L71 L90 (12 DUPLICATES REMOVED)
                 ANSWERS '1-10' FROM FILE MEDLINE
                 ANSWERS '11-19' FROM FILE CAPLUS
                 ANSWERS '20-29' FROM FILE EMBASE
                 ANSWER '30' FROM FILE WPIDS

=> d ibib ab hitstr l99 11-19; d iall 1-10; d iall 20-30

L99  ANSWER 11 OF 30  CAPLUS  COPYRIGHT 2002 ACS       DUPLICATE 1
ACCESSION NUMBER:         2001:78266  CAPLUS
DOCUMENT NUMBER:          134:125957
TITLE:                    Use of N-alkyl derivatives of deoxynojirimycin and
                          glucocerebrosidase for the treatment of glycolipid
                          storage diseases
INVENTOR(S):              Jacob, Gary S.; Dwek, Raymond A.
PATENT ASSIGNEE(S):       G.D. Searle & Co., USA
SOURCE:                   PCT Int. Appl., 27 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2001007078      A1   20010201       WO 2000-US16340   20000724
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
             CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
             LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
             SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
             ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
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     EP 1196190         A1   20020417       EP 2000-946807    20000724
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             IE, SI, LT, LV, FI, RO
     US 2001044453      A1   20011122       US 2001-859928    20010517
     US 2002127213      A1   20020912       US 2002-54802     20020122
PRIORITY APPLN. INFO.:                   US 1999-145568P   P  19990726
                                         US 2000-620026    A3 20000720
                                         WO 2000-US16340   W  20000724
AB   A combination drug therapy is disclosed for the treatment of a patient
```
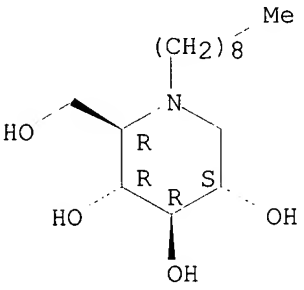

affected with Gaucher's disease or other such glycolipid storage diseases. The method comprises administering a therapeutically effective amt. of both a N-alkyl deriv. of deoxynojirimycin and glucocerebrosidase to alleviate or inhibit the glycolipid storage disease. The alkyl group has from about two to about 20 carbon atoms and preferably is Bu, nonyl or decyl.

IT **81117-35-3**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(deoxynojirimycin N-alkyl derivs. and glucocerebrosidase for the treatment of **Gaucher**'s disease or other glycolipid storage diseases)

RN 81117-35-3 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-nonyl-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

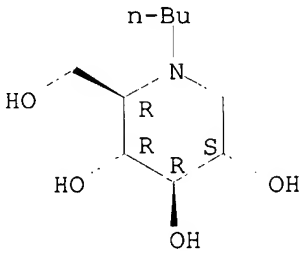
Absolute stereochemistry.



IT **72599-27-0**, N-Butyl-deoxynojirimycin **79206-12-5**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(deoxynojirimycin N-alkyl derivs. and glucocerebrosidase for the treatment of **Gaucher**'s disease or other glycolipid storage diseases)

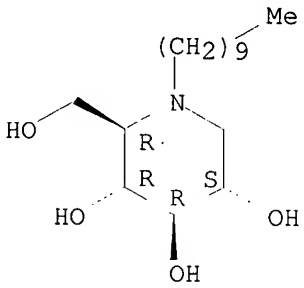
RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79206-12-5 CAPLUS
CN 3,4,5-Piperidinetriol, 1-decyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



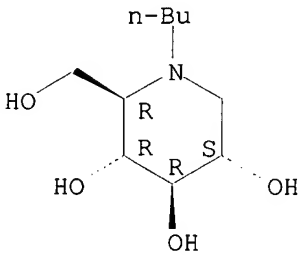
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L99 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
ACCESSION NUMBER: 2001:474848 CAPLUS
DOCUMENT NUMBER: 136:209862
TITLE: Inhibition of substrate synthesis as a strategy for glycolipid lysosomal storage disease therapy
AUTHOR(S): Platt, F. M.; Jeyakumar, M.; Andersson, U.; Priestman, D. A.; Dwek, R. A.; Butters, T. D.; Cox, T. M.; Lachmann, R. H.; Hollak, C.; Aerts, J. M. F. G.; Van Weely, S.; Hrebicek, M.; Moyses, C.; Gow, I.; Elstein, D.; Zimran, A.
CORPORATE SOURCE: Glycobiology Institute, Department of Biochemistry, University of Oxford, Oxford, UK
SOURCE: Journal of Inherited Metabolic Disease (2001), 24(2), 275-290
CODEN: JIMDDP; ISSN: 0141-8955
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The glycosphingolipid (GSL) lysosomal storage diseases are caused by mutations in the genes encoding the glycohydrolases that catabolize GSLs within lysosomes. In these diseases the substrate for the defective enzyme accumulates in the lysosome and the stored GSL leads to cellular dysfunction and disease. The diseases frequently have a progressive neurodegenerative course. The therapeutic options for treating these diseases are relatively limited, and for the majority there are no effective therapies. The problem is further compounded by difficulties in delivering therapeutic agents to the brain. Most research effort to date has focused on strategies for augmenting enzyme levels to compensate for the underlying defect. These include bone marrow transplantation (BMT), enzyme replacement and gene therapy. An alternative strategy that we have been exploring is substrate deprivation. This approach aims to balance the rate of GSL synthesis with the impaired rate of GSL breakdown. The imino sugar N-butyldeoxynojirimycin (NB-DNJ) inhibits the first step in GSL biosynthesis and has been used to evaluate this approach. Studies in an asymptomatic mouse model of Tay-Sachs disease have shown that substrate deprivation prevents GSL storage in the CNS. In a severe neurodegenerative mouse model of Sandhoff disease, substrate deprivation delayed the onset of symptoms and disease progression and significantly increased life expectancy. Combining NB-DNJ and BMT was found to be synergistic in the Sandhoff mouse model. A clin. trial in type I Gaucher disease has been undertaken and has shown beneficial effects. Efficacy was demonstrated on the basis of significant decreases in liver and spleen vols., gradual but significant improvement in hematol. parameters and disease activity markers, together with diminished GSL biosynthesis and storage as detd. by independent biochem. assays. Further trials in type I Gaucher disease are in progress; studies are planned in patients with GSL storage in the CNS.

IT **72599-27-0**, N-Butyldeoxynojirimycin
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(inhibition of substrate synthesis as a strategy for glycolipid lysosomal storage disease therapy)
RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L99 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 2000:756525 CAPLUS
DOCUMENT NUMBER: 133:317560
TITLE: Combination of glucosylceramide synthesis inhibitors and glycolipid degrading enzyme in therapy
INVENTOR(S): Dwek, Raymond A.; Butters, Terence D.; Platt, Frances M.; Priestman, David; Jeyakumar, Mylvaganam
PATENT ASSIGNEE(S): Oxford Glycosciences (Uk) Ltd., UK
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000062779	A1	20001026	WO 2000-GB1560	20000420
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000009913	A	20020108	BR 2000-9913	20000420
EP 1171128	A1	20020116	EP 2000-920920	20000420
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 2001005111	A	20011212	NO 2001-5111	20011019
US 2002142985	A1	20021003	US 2001-42527	20011019

PRIORITY APPLN. INFO.: GB 1999-9066 A 19990420
WO 2000-GB1560 W 20000420

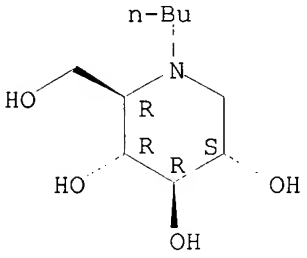
AB The present invention provides the use of an inhibitor of glycolipid synthesis, such as N-butyldeoxynojirimycin (NB-DNJ), N-butyldeoxygalactonojirimycin (NB-DGJ) or N-nonyldeoxynojirimycin (NN-DNJ),

and an agent capable of increasing the rate of glycolipid degrdn. in the manuf. of a medicament for the treatment of a disorder which has at least a component based on glycolipid storage. Such disorders include Gaucher disease, Sandhoff's disease, Fabry's disease,Tay-Sach's disease, Niemann-Pick C storage disease, GM1 gangliosidosis, genetic disorders in which neuronal glycolipid accumulation contributes to the disease's pathol., e.g. mucopolysaccharidoses, neurol. disorders in which glucosylceramide-contg. glycolipid accumulation contributes to the disease's pathol. such as Alzheimer's disease, stroke and epilepsy, cancers of neuronal origin such as glioblastoma and astrocytoma, and cancers originating outside neuronal tissue but presenting with neuronal metastases. For example, Sandhoff mice were bone marrow transplanted (BMT) at 2 wk of age and drug therapy initiated at 9.5-11 wk of age (NB-DNJ 600 mg/kg/day). Survival curves were plotted for each group of animals with each point on the graph representing a death. The untreated group (no BMT, no drug) survived (longest survivor) until 140 days, NB-DNJ only (no BMT) survived until 170 days, BMT only (no NB-DNJ) survived until 200 days, and NB-DNJ plus BMT had extended survival from 200-280 days. The data show synergy approx. 13% above additive.

IT **72599-27-0**, N-Butyldeoxynojirimycin **81117-35-3**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(combination of glucosylceramide synthesis inhibitors and glycolipid degrading enzyme in therapy)

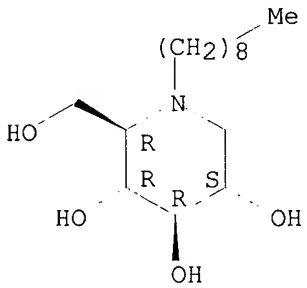
RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 81117-35-3 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-nonyl-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searched by Barb O'Bryen, STIC 308-4291

L99 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
ACCESSION NUMBER: 2000:401653 CAPLUS
DOCUMENT NUMBER: 133:38241
TITLE: Use of long-chain N-alkyl derivatives of deoxynojirimycin for the manufacture of a medicament for the treatment of glycolipid storage diseases
INVENTOR(S): Jacob, Gary S.; Platt, Frances M.; Butters, Terry D.; Dwek, Raymond A.
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; University of Oxford
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000033843	A1	20000615	WO 1999-US27918	19991208
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1137416	A1	20011004	EP 1999-967135	19991208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002531505	T2	20020924	JP 2000-586335	19991208

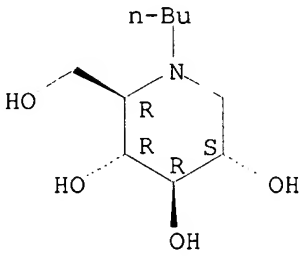
PRIORITY APPLN. INFO.: US 1998-111683P P 19981210
WO 1999-US27918 W 19991208

AB A method is disclosed for the treatment of a patient affected with Gaucher's disease or other such glycolipid storage diseases. The method comprises administering to said patient a therapeutically effective amt. of a long-chain N-alkyl deriv. of deoxynojirimycin to alleviate or inhibit the glycolipid storage disease. The long-chain alkyl group has from nine to about 20 carbon atoms and preferably is nonyl or decyl.

IT **72599-27-0**, N-Butyldeoxynojirimycin
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(deoxynojirimycin long-chain N-alkyl derivs. for treatment of glycolipid storage diseases)

RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

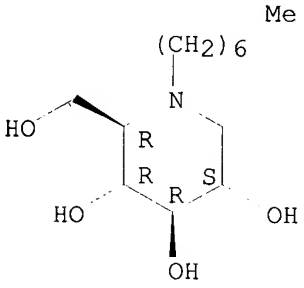
Absolute stereochemistry.



IT **72458-45-8 79206-10-3 79206-12-5**
79206-22-7 81117-35-3 121133-60-6
274902-52-2 274902-53-3
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(deoxynojirimycin long-chain N-alkyl derivs. for treatment of glycolipid storage diseases)

RN 72458-45-8 CAPLUS
CN 3,4,5-Piperidinetriol, 1-heptyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79206-10-3 CAPLUS
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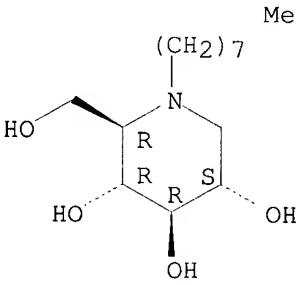
Absolute stereochemistry.



RN 79206-12-5 CAPLUS
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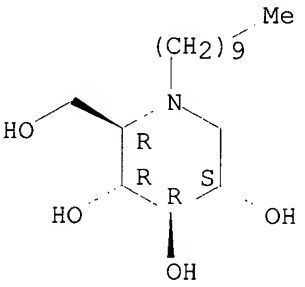
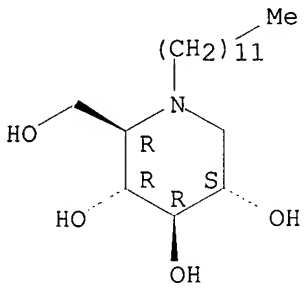
Absolute stereochemistry.



RN 79206-22-7 CAPLUS

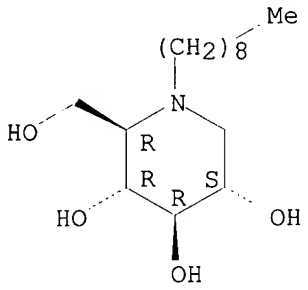
CN 3,4,5-Piperidinetriol, 1-dodecyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 81117-35-3 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-nonyl-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 121133-60-6 CAPLUS
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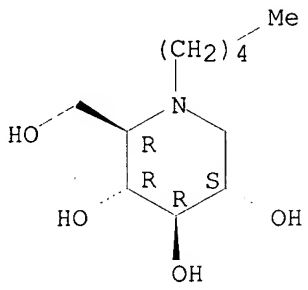
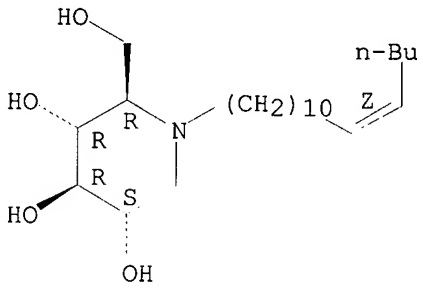
Absolute stereochemistry.



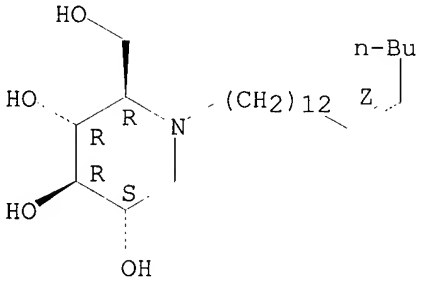
RN 274902-52-2 CAPLUS
CN 3,4,5-Piperidinetriol, 1-(11Z)-11-hexadecenyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 274902-53-3 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-(13Z)-13-octadecenyl-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

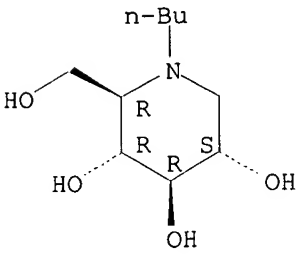
Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L99 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
ACCESSION NUMBER: 2000:847070 CAPLUS
DOCUMENT NUMBER: 134:125918
TITLE: Imino sugar therapy for type 1 **Gaucher** disease
AUTHOR(S): Priestman, David A.; Platt, Frances M.; Dwek, Raymond A.; Butters, Terry D.
CORPORATE SOURCE: Glycobiology Institute, Department of Biochemistry, University of Oxford, Oxford, OX1 3QU, UK
SOURCE: Glycobiology (2000), 10(11), iv-vi
CODEN: GLYCE3; ISSN: 0959-6658
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Infused .beta.-glucocerebrosidase activity was not inhibited in mice treated with N-butyldeoxynojirimycin, an inhibitor of glycosphingolipid synthesis.
IT **72599-27-0**, N-Butyldeoxynojirimycin
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(effect of N-butyldeoxynojirimycin on serum .beta.-glucocerebrosidase activity)
RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L99 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 8
ACCESSION NUMBER: 1995:312535 CAPLUS
DOCUMENT NUMBER: 122:81897
TITLE: Preparation of N-alkyldeoxygalactonojirimycins as glycolipid biosynthesis inhibitors.
INVENTOR(S): Platt, Frances M.; Neises, Gabrielle R.; Dwek, Raymond A.; Butters, Terry D.
PATENT ASSIGNEE(S): G.D Searle and Co., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9426714	A1	19941124	WO 1994-US4974	19940511
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5399567	A	19950321	US 1993-61645	19930513
US 6291657	B1	20010918	US 1993-102654	19930805
AU 9467832	A1	19941212	AU 1994-67832	19940511
EP 698012	A1	19960228	EP 1994-916021	19940511
EP 698012	B1	19970129		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08510244	T2	19961029	JP 1994-525541	19940511
US 5525616	A	19960611	US 1995-439842	19950512
US 5801185	A	19980901	US 1997-782322	19970113

PRIORITY APPLN. INFO.:
US 1993-61645 A 19930513
US 1993-102654 A 19930805
WO 1994-US4974 W 19940511
US 1994-321718 A3 19941012
US 1995-393640 A1 19950224
US 1996-650558 A1 19960520

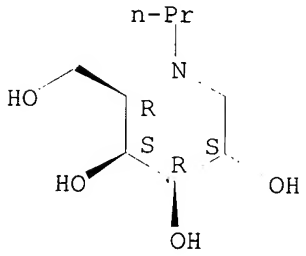
AB Novel N-alkyl derivs. of deoxygalactonojirimycin in which said alkyl contains 3-6 C atoms were prepd. These novel compds. are useful for selectively inhibiting glycolipid synthesis. Thus, deoxygalactononojirimycin, butyraldehyde, and Pd black were stirred in aq. NaOAc buffer at pH 5.0 under H for 16 h at 20.degree. to give N-butyldeoxygalactonojirimycin (NB-DGJ). NB-DGJ reduced binding of cholera toxin to H9 cells by approx. 70%, consistent with the loss of GM1 from the cell surface.

IT **141206-24-8P 141206-42-0P 158100-26-6P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU**

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-alkyldeoxygalactonojirimycins as glycolipid synthesis inhibitors)

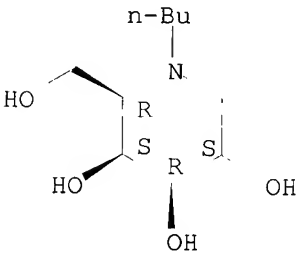
RN 141206-24-8 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-propyl-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



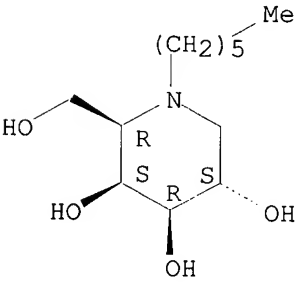
RN 141206-42-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 158100-26-6 CAPLUS
CN 3,4,5-Piperidinetriol, 1-hexyl-2-(hydroxymethyl)-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L99 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:687476 CAPLUS
DOCUMENT NUMBER: 135:236444
TITLE: N-alkyl deoxygalactonojirimycin derivatives for inhibition of glycolipid synthesis
INVENTOR(S): Platt, Frances M.; Neises, Gabrielle R.; Dwek, Raymond

Searched by Barb O'Bryen, STIC 308-4291

A.; Butters, Terry D.
PATENT ASSIGNEE(S): Monsanto Company, USA
SOURCE: U.S., 19 pp., Cont.-in-part of U.S. 5,399,567.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6291657	B1	20010918	US 1993-102654	19930805
US 5399567	A	19950321	US 1993-61645	19930513
CA 2159988	AA	19941124	CA 1994-2159988	19940511
WO 9426714	A1	19941124	WO 1994-US4974	19940511
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9467832	A1	19941212	AU 1994-67832	19940511
EP 698012	A1	19960228	EP 1994-916021	19940511
EP 698012	B1	19970129		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08510244	T2	19961029	JP 1994-525541	19940511
AT 148456	E	19970215	AT 1994-916021	19940511
ES 2097653	T3	19970401	ES 1994-916021	19940511
US 5472969	A	19951205	US 1994-321718	19941012
US 5580884	A	19961203	US 1995-396989	19950301
US 5525616	A	19960611	US 1995-439842	19950512
US 5786368	A	19980728	US 1996-588027	19960117
US 5798366	A	19980825	US 1997-782321	19970113
US 5801185	A	19980901	US 1997-782322	19970113

PRIORITY APPLN. INFO.:

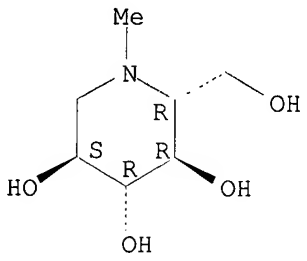
US 1993-61645	A2	19930513
US 1993-102654	A	19930805
WO 1994-US4974	W	19940511
US 1994-321718	A3	19941012
US 1995-393640	A2	19950224
US 1995-396989	A3	19950301
US 1996-588027	A2	19960117
US 1996-650558	A1	19960520

AB N-(C3-6)alkyl derivs. of deoxygalactonojirimycin are provided. These compds. are useful for selectively inhibiting glycolipid synthesis. N-butyldeoxygalactonojirimycin was prepd. from deoxygalactonojirimycin and butyraldehyde.

IT **69567-10-8 72458-42-5 72458-43-6**
72599-27-0, N-Butyldeoxynojirimycin **81117-34-2**
105308-35-8 141206-22-6 141206-23-7
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(N-alkyl deoxygalactonojirimycin derivs. for inhibition of glycolipid synthesis)

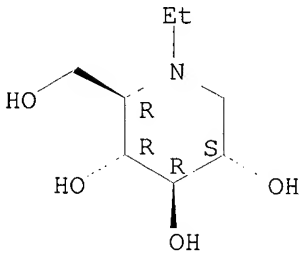
RN 69567-10-8 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-methyl-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



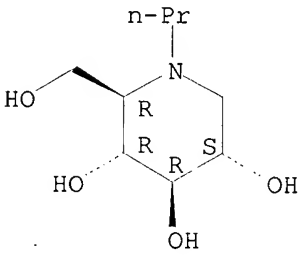
RN 72458-42-5 CAPLUS
CN 3,4,5-Piperidinetriol, 1-ethyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



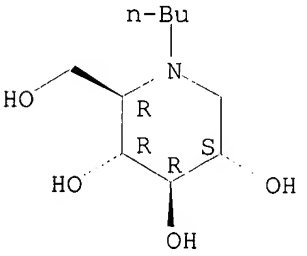
RN 72458-43-6 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-propyl-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



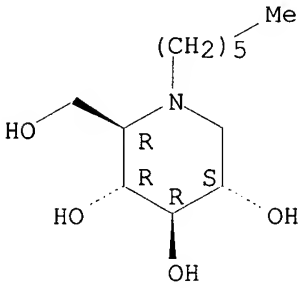
RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



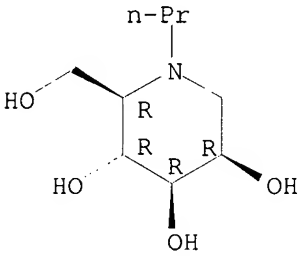
RN 81117-34-2 CAPLUS
CN 3,4,5-Piperidinetriol, 1-hexyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



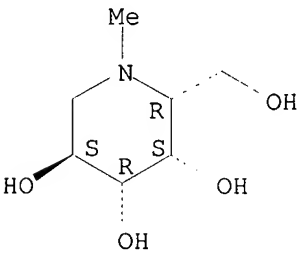
RN 105308-35-8 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-propyl-, (2R,3R,4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



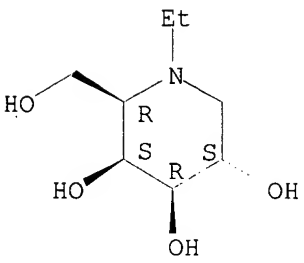
RN 141206-22-6 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-methyl-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



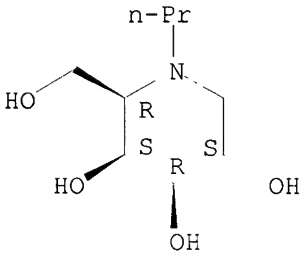
RN 141206-23-7 CAPLUS
CN 3,4,5-Piperidinetriol, 1-ethyl-2-(hydroxymethyl)-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



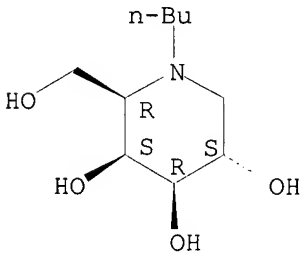
IT **141206-24-8P 141206-42-0P 158100-26-6P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(N-alkyl deoxygalactonojirimycin derivs. for inhibition of glycolipid synthesis)
RN 141206-24-8 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-propyl-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



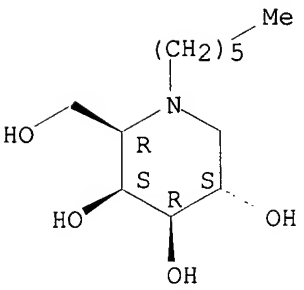
RN 141206-42-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 158100-26-6 CAPLUS
CN 3,4,5-Piperidinetriol, 1-hexyl-2-(hydroxymethyl)-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L99 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:183999 CAPLUS
DOCUMENT NUMBER: 132:329434
TITLE: Molecular requirements of imino sugars for the selective control of N-linked glycosylation and glycosphingolipid biosynthesis
AUTHOR(S): Butters, T. D.; Van den Broek, L. A. G. M.; Fleet, G. W. J.; Krulle, T. M.; Wormald, M. R.; Dwek, R. A.; Platt, F. M.
CORPORATE SOURCE: Glycobiology Institute, Department of Biochemistry, Oxford University, Oxford, OX1 3QU, UK
SOURCE: Tetrahedron: Asymmetry (2000), 11(1), 113-124
CODEN: TASYE3; ISSN: 0957-4166
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

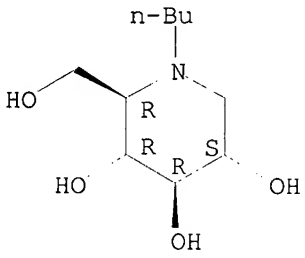
AB N-Butyl-deoxynojirimycin (NB-DNJ) has been approved for clin. trials as a potential therapy for Gaucher disease, a glycolipid lysosomal storage disorder. As this compd. has both glycoprotein processing .alpha.-glucosidase and ceramide glucosyltransferase inhibitory activity, we have sought to det. the mol. basis for these two activities. NB-DNJ is known to resemble the pos. charged oxocarbonium-like transition state for .alpha.-glucosidase I and the structure-function relationships we present now help to define the recognition epitope for the enzyme. Inhibition of ceramide glucosyltransferase by NB-DNJ was competitive for ceramide (Ki=7.4 .mu.M) and non-competitive for UDP-glucose, indicating inhibitory activity is by ceramide mimicry. The presence of an N-alkyl chain was obligatory for transferase inhibition and increases in alkyl chain length provided a modest increase in inhibitory potency. By contrast, .alpha.-glucosidase inhibition was independent of the N-alkyl chain and changes in chain length. The effects of ring substitutions identified the C3 hydroxyl group as being crit. for both enzymes but C1 and C6 modifications led to a loss of transferase inhibition only. Attempts to rationalize these data for transferase inhibition using an energy minimized mol. model of NB-DNJ and ceramide predicted structural homol. of three stereogenic centers and the N-alkyl chain of NB-DNJ, with the trans-alkenyl and N-acyl chain of ceramide. On the basis of these studies, modifications to imino sugar inhibitors can be suggested that allow a more selective approach for mol. inhibition of both ceramide glucosyltransferase and .alpha.-glucosidase I, leading to improved compds. for the potential treatment of lysosomal glycosphingolipid storage disorders and viral infections, resp.

IT **72599-27-0 79206-12-5 141206-42-0 210708-42-2 267668-04-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(mol. requirements of imino sugars for the selective control of N-linked glycosylation and glycosphingolipid biosynthesis)

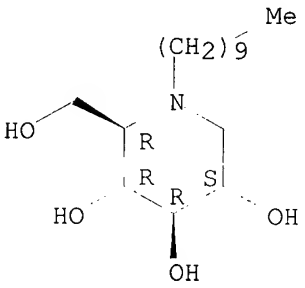
RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



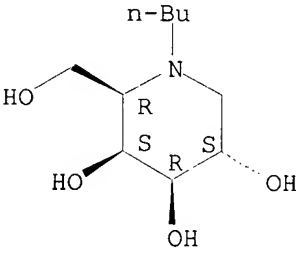
RN 79206-12-5 CAPLUS
CN 3,4,5-Piperidinetriol, 1-decyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



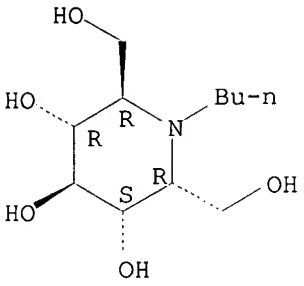
RN 141206-42-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3S,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



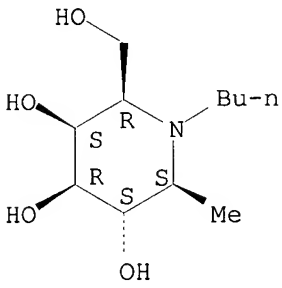
RN 210708-42-2 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2,6-bis(hydroxymethyl)-, stereoisomer (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 267668-04-2 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-6-methyl-, (2R,3S,4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L99 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:390377 CAPLUS
DOCUMENT NUMBER: 131:39716
TITLE: Glucosidase or glucosyltransferase inhibitors for inhibition of membrane-associated viral replication and treatment of lipid storage diseases
INVENTOR(S): Blumberg, Baruch S.; Block, Timothy M.; Dwek, Raymond A.; Mehta, Anand; Platt, Frances; Butters, Terry D.; Zitzmann, Nicole
PATENT ASSIGNEE(S): The Chancellor, Masters and Scholars of the University of Oxford, UK; Thomas Jefferson University
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929321	A1	19990617	WO 1998-US26241	19981210

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,

CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2312423	AA	19990617	CA 1998-2312423	19981210
AU 9917215	A1	19990628	AU 1999-17215	19981210
EP 1037636	A1	20000927	EP 1998-962046	19981210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9813508	A	20001003	BR 1998-13508	19981210
JP 2001525367	T2	20011211	JP 2000-523992	19981210

PRIORITY APPLN. INFO.: US 1997-69245P P 19971211
WO 1998-US26241 W 19981210

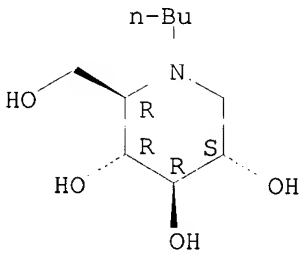
OTHER SOURCE(S): MARPAT 131:39716

AB Methods are disclosed for inhibiting morphogenesis of host cell membrane-budding viruses and infections caused thereby, using compds. that inhibit host cell glucosidase or glucosyltransferase enzymes. Methods are also disclosed for treating lipid storage diseases using compds. that inhibit glucosyltransferase enzymes.

IT **72599-27-0 81117-35-3**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glucosidase or glucosyltransferase inhibitors for inhibition of membrane-assocd. viral replication and treatment of lipid storage diseases)

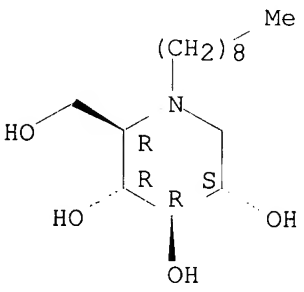
RN 72599-27-0 CAPLUS
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 81117-35-3 CAPLUS
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-nonyl-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L99 ANSWER 1 OF 30 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000259106 MEDLINE
DOCUMENT NUMBER: 20259106 PubMed ID: 10801168
TITLE: Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis.
COMMENT: Comment in: Lancet. 2000 Aug 19;356(9230):676-7
Comment in: Lancet. 2000 Aug 19;356(9230):677
AUTHOR: Cox T; Lachmann R; Hollak C; Aerts J; van Weely S; Hrebicek M; Platt F; Butters T; Dwek R; Moyses C; Gow I; Elstein D; Zimran A
CORPORATE SOURCE: Department of Medicine, University of Cambridge, Addenbrooke's Hospital, UK.
SOURCE: LANCET, (2000 Apr 29) 355 (9214) 1481-5.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000606
Last Updated on STN: 20020208
Entered Medline: 20000522

ABSTRACT:
BACKGROUND: Current treatment for Gaucher's disease involves administration of intravenous glucocerebrosidase to degrade glucocerebroside stored in lysosomes. Lowering the rate of biosynthesis of glucocerebroside should decrease accumulation of this substrate. We investigated the safety and efficacy of OGT 918 (N-butyldeoxynojirimycin), an inhibitor of glucosyltransferase, as a novel oral treatment for non-neuronopathic Gaucher's disease. METHODS: We recruited, into a 1-year open-label study, 28 adults (seven with previous splenectomies) from four national Gaucher's referral clinics, who were unable or unwilling to receive enzyme treatment. We measured liver and spleen volume by computed tomography or magnetic resonance imaging at baseline and at months 6 and 12, and biochemical and haematological variables monthly, including chitotriosidase activity (a sensitive marker of Gaucher's disease activity). Patients were started on 100 mg oral OGT 918 three times daily. FINDINGS: Baseline liver volumes were 1.1-2.7 times normal and spleen volumes 5.1-24.8 times normal. At 12 months, mean liver and spleen volumes were significantly lowered by 12% (95% CI 7.8-16.4) and 19% (14.3-23.7), respectively (each $p<0.001$). Haematological variables improved slightly. Mean organ volume and blood counts improved continually between 6 months and 12 months of treatment. Mean chitotriosidase concentrations fell by 16.4% over 12 months ($p<.0001$). Six patients withdrew because of gastrointestinal complaints (two), personal reasons (two), or severe pre-existing disease (two). The most frequent adverse effect was diarrhoea, which occurred in 79% of patients shortly after the start of treatment. INTERPRETATION: Decrease of substrate formation by OGT 918 improves key clinical features of non-neuronopathic Gaucher's disease. The strategy justifies further trials in this and other glycosphingolipid storage disorders.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
1-Deoxynojirimycin: AE, adverse effects
***1-Deoxynojirimycin: AA, analogs & derivatives**
1-Deoxynojirimycin: PK, pharmacokinetics
1-Deoxynojirimycin: TU, therapeutic use
Administration, Oral
Adult
Aged
Diarrhea: CI, chemically induced
Enzyme Inhibitors: AE, adverse effects
Enzyme Inhibitors: PK, pharmacokinetics

*Enzyme Inhibitors: TU, therapeutic use
***Gaucher Disease: DT, drug therapy**
*Glucosyltransferases: AI, antagonists & inhibitors
Half-Life
Hexosaminidases: BL, blood
Liver: DE, drug effects
Magnetic Resonance Imaging
Middle Age
Spleen: DE, drug effects
Tomography, X-Ray Computed

CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0 (n-butyldeoxynojirimycin)** structure printed at end

CHEMICAL NAME: 0 (Enzyme Inhibitors); EC 2.4.1.- (Glucosyltransferases); EC 3.2.1.- (Hexosaminidases); EC 3.2.1.- (chitotriosidase)

L99 ANSWER 2 OF 30 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999155079 MEDLINE
DOCUMENT NUMBER: 99155079 PubMed ID: 10037475
TITLE: Differential effects of glycolipid biosynthesis inhibitors on ceramide-induced cell death in neuroblastoma cells.
AUTHOR: Bieberich E; Freischutz B; Suzuki M; Yu R K
CORPORATE SOURCE: Department of Biochemistry and Molecular Biophysics, Medical College of Virginia of Virginia Commonwealth University, Richmond 23298-0614, USA.
CONTRACT NUMBER: NS 11853-24 (NINDS)
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1999 Mar) 72 (3) 1040-9. Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 20000303
Entered Medline: 19990318

ABSTRACT:
An in vitro model of Gaucher's disease in murine neuroblastoma x rat glioma NG108-15 cells was used to investigate the physiological effects of two specific inhibitors of glucosylceramide synthase, d,l-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (d,l-PDMP) and N-butyldeoxynojirimycin (NB-DNJ), which have been suggested as agents for treatment of glycolipid storage disorders. Incubation of NG108-15 cells with conduritol-B-epoxide, a covalent inhibitor of glucosylceramidase, raised the intracellular concentration of glucosylceramide (GC) by more than fourfold, indicating a glycolipid composition equivalent to that of Gaucher's cells. The level of GC was decreased, and the cells were depleted of gangliosides by postincubation with d,l-PDMP or NB-DNJ. Treatment with d,l-PDMP, but not with NB-DNJ, resulted in a dose-dependent reduction of the growth rate and eventually caused cell death in NG108-15 cells on reaching confluency. An in situ detection assay using terminal nucleotidyltransferase indicated that cell degeneration was accompanied by apoptosis. Lipid analysis by high-performance TLC revealed that on incubation with d,l-PDMP, but not with NB-DNJ, the concentration of endogenous ceramide was elevated by threefold. Ceramide elevation and apoptosis were also observed when NG108-15 cells were incubated with daunorubicin, which was previously reported to induce programmed cell death by stimulation of ceramide synthesis. Structural characterization by HPLC and subsequent laser desorption mass spectrometry revealed that the endogenous ceramide contained fatty acids with chain lengths ranging from C14:0 to C24:0. The results indicate that elevation of levels of these ceramide species by incubation with d,l-PDMP or daunorubicin induces programmed cell death in NG108-15 cells. Because ceramide accumulation and cell death were not observed on incubation with NB-DNJ, its use is suggested to be less toxic than that of d,l-PDMP for treatment of Gaucher's disease and other sphingolipid storage disorders.

CONTROLLED TERM: Check Tags: Animal; Support, U.S. Gov't, P.H.S.
1-Deoxynojirimycin: AA, analogs & derivatives
1-Deoxynojirimycin: PD, pharmacology
Apoptosis: DE, drug effects
Brain Neoplasms: ME, metabolism
*Brain Neoplasms: PA, pathology
Cell Death: DE, drug effects
Cell Division: DE, drug effects
Ceramides: ME, metabolism
*Ceramides: PH, physiology
Ceramides: TO, toxicity
Enzyme Inhibitors: PD, pharmacology
Gaucher Disease: ME, metabolism
***Gaucher Disease: PA, pathology**
Glucosylceramides: AI, antagonists & inhibitors
Glucosyltransferases: AI, antagonists & inhibitors
*Glycolipids: AI, antagonists & inhibitors
Glycolipids: BI, biosynthesis
Mice
Morpholines: PD, pharmacology
Neuroblastoma: ME, metabolism
*Neuroblastoma: PA, pathology
Rats
Tumor Cells, Cultured

CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0 (n-butyldeoxynojirimycin)**; 73257-80-4 (RV 538)

CHEMICAL NAME: 0 (Ceramides); 0 (Enzyme Inhibitors); 0 (Glucosylceramides); 0 (Glycolipids); 0 (Morpholines); EC 2.4.1.- (Glucosyltransferases); EC 2.4.1.80 (ceramide glucosyltransferase)

L99 ANSWER 3 OF 30 MEDLINE DUPLICATE 9

ACCESSION NUMBER: 95014583 MEDLINE

DOCUMENT NUMBER: 95014583 PubMed ID: 7929454

TITLE: N-butyldeoxygalactonojirimycin inhibits glycolipid biosynthesis but does not affect N-linked oligosaccharide processing.

AUTHOR: Platt F M; Neises G R; Karlsson G B; Dwek R A; Butters T D

CORPORATE SOURCE: Department of Biochemistry, University of Oxford, United Kingdom.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Oct 28) 269 (43) 27108-14.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199411

ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 20000303
Entered Medline: 19941123

ABSTRACT:
We have previously reported that the imino sugar N-butyldeoxynojirimycin (NB-DNJ) inhibits glycolipid biosynthesis, in addition to its known activity as an inhibitor of the N-linked oligosaccharide processing enzyme alpha-glucosidase I. In an attempt to dissociate these two activities and identify an inhibitor which was more selective for the glycolipid biosynthetic pathway, several imino sugars have been N-alkylated and tested for inhibitory activity. The galactose analogue N-butyldeoxygalactonojirimycin (NB-DGJ) was found to be a potent inhibitor of glycolipid biosynthesis but in contrast to NB-DNJ had no effect on the maturation of N-linked oligosaccharides or on lysosomal glucocerebrosidase. The effect of increasing N-alkyl chain length on

glycolipid inhibition was investigated. Nonalkylated DGJ, the N-methyl and N-ethyl derivatives, were noninhibitory. However, N-propylation resulted in partial inhibition while the N-butyl and N-hexyl derivatives resulted in maximal inhibition. Increasing alkyl chain length also resulted in increased potency of glucosyltransferase inhibition. In an in vitro Gaucher's disease model NB-DGJ was as effective as NB-DNJ in preventing glycolipid storage and may represent a more selective potential therapeutic agent than NB-DNJ for the management of this and other glycosphingolipidoses.

CONTROLLED TERM: Check Tags: Animal; Comparative Study; Human; Support, Non-U.S. Gov't
***1-Deoxynojirimycin: AA, analogs & derivatives**
1-Deoxynojirimycin: PD, pharmacology
Cells, Cultured
Disease Models, Animal
Gaucher Disease: ME, metabolism
Glucosylceramidase: DE, drug effects
Glucosyltransferases: AI, antagonists & inhibitors
*Glycolipids: BI, biosynthesis
Mice
*Oligosaccharides: BI, biosynthesis
Structure-Activity Relationship
alpha-Glucosidases: DE, drug effects
CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0 (n-butyldeoxynojirimycin)**
CHEMICAL NAME: 0 (Glycolipids); 0 (N-butyldeoxygalactonojirimycin); 0 (Oligosaccharides); EC 2.4.1.- (Glucosyltransferases); EC 2.4.1.80 (ceramide glucosyltransferase); EC 3.2.1.20 (alpha-Glucosidases); EC 3.2.1.45 (Glucosylceramidase)

L99 ANSWER 4 OF 30 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 94179218 MEDLINE
DOCUMENT NUMBER: 94179218 PubMed ID: 8132559
TITLE: N-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis.
AUTHOR: Platt F M; Neises G R; Dwek R A; Butters T D
CORPORATE SOURCE: Department of Biochemistry, University of Oxford, United Kingdom.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Mar 18) 269 (11) 8362-5.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940428
Last Updated on STN: 20000303
Entered Medline: 19940418

ABSTRACT:
The imino sugar deoxynojirimycin and its alkylated derivatives are inhibitors of the N-linked oligosaccharide processing enzymes alpha-glucosidase I and II. These compounds are glucose analogues and have the potential to inhibit both glucosidases and glucosyltransferases. However, to date there has been no report of deoxynojirimycin or similar analogues inhibiting a mammalian glucosyltransferase. We have investigated the effects of deoxynojirimycin and its alkylated derivatives on the biosynthesis of glycolipids in HL-60 cells. We have found that the N-butyl and N-hexyl derivatives of deoxynojirimycin, but not deoxynojirimycin itself, are novel inhibitors of the glucosyltransferase-catalyzed biosynthesis of glucosylceramide. This results in the inhibition of biosynthesis of all glucosylceramide-based glycosphingolipids. We have investigated the ability of one of these compounds, N-butyldeoxynojirimycin, to offset glucosylceramide accumulation in an in vitro Gaucher's disease model.

This compound prevents lysosomal glycolipid storage and offers a novel therapeutic approach for the management of this and other glycolipid storage disorders.

CONTROLLED TERM: Check Tags: Animal; Comparative Study; Human; Support, Non-U.S. Gov't
***1-Deoxynojirimycin: AA, analogs & derivatives**
1-Deoxynojirimycin: PD, pharmacology
Cell Line
Gaucher Disease
Glucosyltransferases: AI, antagonists & inhibitors
Glycolipids: AI, antagonists & inhibitors
*Glycolipids: BI, biosynthesis
Lysosomes: DE, drug effects
Lysosomes: UL, ultrastructure
Macrophages: DE, drug effects
Macrophages: ME, metabolism
Macrophages: UL, ultrastructure
Mice
Models, Biological
Structure-Activity Relationship
Tumor Cells, Cultured
*alpha-Glucosidases: AI, antagonists & inhibitors
CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0 (n-butyldeoxynojirimycin)**
CHEMICAL NAME: 0 (Glycolipids); EC 2.4.1.- (Glucosyltransferases); EC 3.2.1.20 (alpha-Glucosidases)

L99 ANSWER 5 OF 30 MEDLINE
ACCESSION NUMBER: 2000438897 MEDLINE
DOCUMENT NUMBER: 20421664 PubMed ID: 10968454
TITLE: Treatment of Gaucher's disease with OGT 918.
COMMENT: Comment on: Lancet. 2000 Apr 29;355(9214):1481-5
AUTHOR: Mistry P K
SOURCE: LANCET, (2000 Aug 19) 356 (9230) 676-7.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20020208
Entered Medline: 20000920
CONTROLLED TERM: Check Tags: Human
***1-Deoxynojirimycin: AE, adverse effects**
1-Deoxynojirimycin: AA, analogs & derivatives
***1-Deoxynojirimycin: TU, therapeutic use**
*Enzyme Inhibitors: AE, adverse effects
*Enzyme Inhibitors: TU, therapeutic use
***Gaucher Disease: DT, drug therapy**
Gaucher Disease: ME, metabolism
Glucosylceramidase: TU, therapeutic use
Glucosylceramides: ME, metabolism
Hepatomegaly: DT, drug therapy
Hepatomegaly: ET, etiology
Hexosaminidases: BL, blood
Splenomegaly: DT, drug therapy
Splenomegaly: ET, etiology
Time
alpha-Glucosidases: AI, antagonists & inhibitors
CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0**

(n-butyldeoxynojirimycin)
CHEMICAL NAME: 0 (Enzyme Inhibitors); 0 (Glucosylceramides); EC 3.2.1.- (Hexosaminidases); EC 3.2.1.- (chitotriosidase); EC 3.2.1.20 (alpha-Glucosidases); EC 3.2.1.45 (Glucosylceramidase)

L99 ANSWER 6 OF 30 MEDLINE
ACCESSION NUMBER: 2000438898 MEDLINE
DOCUMENT NUMBER: 20421665 PubMed ID: 10968455
TITLE: Treatment of Gaucher's disease with OGT 918.
COMMENT: Comment on: Lancet. 2000 Apr 29;355(9214):1481-5
AUTHOR: Kranda M
SOURCE: LANCET, (2000 Aug 19) 356 (9230) 677.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20020208
Entered Medline: 20000920
CONTROLLED TERM: Check Tags: Human
***1-Deoxynojirimycin: AD, administration & dosage**
***1-Deoxynojirimycin: AE, adverse effects**
1-Deoxynojirimycin: AA, analogs & derivatives
Administration, Oral
*Enzyme Inhibitors: AD, administration & dosage
*Enzyme Inhibitors: AE, adverse effects
***Gaucher Disease: DT, drug therapy**
Gaucher Disease: ME, metabolism
Randomized Controlled Trials
Time
Treatment Outcome
alpha-Glucosidases: AI, antagonists & inhibitors
CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0 (n-butyldeoxynojirimycin)**
CHEMICAL NAME: 0 (Enzyme Inhibitors); EC 3.2.1.20 (alpha-Glucosidases)

L99 ANSWER 7 OF 30 MEDLINE
ACCESSION NUMBER: 2000514093 MEDLINE
DOCUMENT NUMBER: 20523197 PubMed ID: 11073045
TITLE: Risks of Gaucher's treatment.
AUTHOR: Barranger J A
SOURCE: LANCET, (2000 Oct 14) 356 (9238) 1353-4.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001129
CONTROLLED TERM: Check Tags: Human
1-Deoxynojirimycin: AE, adverse effects
***1-Deoxynojirimycin: AA, analogs & derivatives**
1-Deoxynojirimycin: TU, therapeutic use
Anti-HIV Agents: AE, adverse effects
*Anti-HIV Agents: TU, therapeutic use
Dose-Response Relationship, Drug
***Gaucher Disease: DT, drug therapy**

Risk Factors
CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0 (n-butyldeoxynojirimycin)**
CHEMICAL NAME: 0 (Anti-HIV Agents)

L99 ANSWER 8 OF 30 MEDLINE
ACCESSION NUMBER: 2001144394 MEDLINE
DOCUMENT NUMBER: 20586230 PubMed ID: 11221677
TITLE: Imino sugar therapy for type 1 Gaucher disease.
AUTHOR: Priestman D A; Platt F M; Dwek R A; Butters T D
SOURCE: GLYCOBIOLOGY, (2000 Nov) 10 (11) iv-vi.
Journal code: 9104124. ISSN: 0959-6658.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010202
CONTROLLED TERM: Check Tags: Animal; Human
1-Deoxynojirimycin: AD, administration & dosage
***1-Deoxynojirimycin: AA, analogs & derivatives**
1-Deoxynojirimycin: TU, therapeutic use
Enzyme Inhibitors: AD, administration & dosage
*Enzyme Inhibitors: TU, therapeutic use
***Gaucher Disease: DT, drug therapy**
Gaucher Disease: ME, metabolism
Glucosylceramidase: AD, administration & dosage
Glucosylceramidase: BL, blood
Glycosphingolipids: ME, metabolism
Mice
*alpha-Glucosidases: AI, antagonists & inhibitors
CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); **72599-27-0 (n-butyldeoxynojirimycin)**
CHEMICAL NAME: 0 (Enzyme Inhibitors); 0 (Glycosphingolipids); EC 3.2.1.20 (alpha-Glucosidases); EC 3.2.1.45 (Glucosylceramidase)

L99 ANSWER 9 OF 30 MEDLINE
ACCESSION NUMBER: 87299749 MEDLINE
DOCUMENT NUMBER: 87299749 PubMed ID: 2956992
TITLE: Human acid beta-glucosidase: use of inhibitors, alternative substrates and amphiphiles to investigate the properties of the normal and Gaucher disease active sites.
AUTHOR: Osiecki-Newman K; Fabbro D; Legler G; Desnick R J; Grabowski G A
CONTRACT NUMBER: K04 AM01351 (NIADDK)
R01 AM 26729 (NIADDK)
RR-71 (NCRR)
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1987 Sep 2) 915 (1) 87-100.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198710
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 20000303
Entered Medline: 19871013
ABSTRACT:
Comparative studies with lipoidal inhibitors and alternative substrates were conducted to investigate the properties of the active site of human acid beta-glucosidase (D-glucosyl-N-acylsphingosine glucohydrolase, EC 3.2.1.45)

from normal placenta and spleens of Type 1 Ashkenazi Jewish Gaucher disease (AJGD) patients. With the normal enzyme, the inhibitory potencies of series of alkyl(Cn; n = 0-18)amines, alkyl beta-glucosides and alkyl-1-deoxynojirimycins were a biphasic function of increasing chain length: i.e., large decreases in Ki,app or IC50 were found only with n greater than 4 and limiting values were approached with n = 12-14. This biphasic function of alkyl chain length was observed in the presence or absence of detergents and/or negatively charged lipids. In the presence of Triton X-100 concentrations greater than the critical micellar concentration, the relative (to deoxynojirimycin) inhibitory potencies of the N-Cn-deoxynojirimycins (n greater than 4) were decreased about 3-5-fold, due to an energy requirement to extract the inhibitors from Triton X-100 micelles. The Ki,app or IC50 of N-hexylglucosylsphingosine was inversely related to the Triton X-100 concentration and was not affected by the presence of 'co-glucosidase'. The mutual exclusion of glucon, N-Cn-deoxynojirimycin and sphingosine derivatives from the normal enzyme suggested a shared region for binding in the active site. Increasing the fatty-acid acyl chain length of glucosyl ceramide from 1 to 24 carbons had minor effects on Km,app (= Kis,app) (8-40 microM), but increased Vmax,app up to 13-fold. With the AJGD enzyme, the inhibitor and alternative substrate findings were similar to those with the normal enzyme, except that Kis,app(AJGD)/Kis,app(normal) = 4 to 11 for the Cn-glycons and sphingosine derivatives. These results indicated that (1) the Ki,app or Km,app values for amphiphilic inhibitors or substrates reflect a balance of binding energies for two hydrophobic subsites within the enzyme's active site and Triton X-100 micelles and (2) the abnormal properties of the AJGD enzyme result from an amino-acid alteration(s) within or near a hydrophilic region which is shared by the glycon-binding site and the two hydrophobic sites of the active site.

CONTROLLED TERM: Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
1-Deoxynojirimycin
Amines: PD, pharmacology
Binding Sites
Binding, Competitive
Ceramides: ME, metabolism
***Gaucher Disease: EN, enzymology**
Glucosamine: AA, analogs & derivatives
Glucosamine: PD, pharmacology
*Glucosidases: ME, metabolism
Glucosides: PD, pharmacology
Kinetics
Octoxynol
Placenta: EN, enzymology
Polyethylene Glycols: PD, pharmacology
Pregnancy
Sphingosine: AA, analogs & derivatives
Sphingosine: PD, pharmacology
Spleen: EN, enzymology
Structure-Activity Relationship
beta-Glucosidase: AI, antagonists & inhibitors
*beta-Glucosidase: ME, metabolism

CAS REGISTRY NO.: 123-78-4 (Sphingosine); 19130-96-2 (1-Deoxynojirimycin); 3416-24-8 (Glucosamine); 9002-93-1 (Octoxynol)

CHEMICAL NAME: 0 (Amines); 0 (Ceramides); 0 (Glucosides); 0 (Polyethylene Glycols); EC 3.2.1.- (Glucosidases); EC 3.2.1.21 (beta-Glucosidase)

L99 ANSWER 10 OF 30 MEDLINE

ACCESSION NUMBER: 87004496 MEDLINE

DOCUMENT NUMBER: 87004496 PubMed ID: 2944742

TITLE: Human acid beta-glucosidase: affinity purification of the normal placental and Gaucher disease splenic enzymes on N-alkyl-deoxynojirimycin-sepharose.

AUTHOR: Osiecki-Newman K M; Fabbro D; Dinur T; Boas S; Gatt S; Legler G; Desnick R J; Grabowski G A
CONTRACT NUMBER: AM 36729 (NIADDK)
K04-AM 01351 (NIADDK)
SOURCE: ENZYME, (1986) 35 (3) 147-53.
Journal code: 1262265. ISSN: 0013-9432.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198610
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 20000303
Entered Medline: 19861030

ABSTRACT:
Two sepharose-bound 1-deoxynojirimycin N-alkyl derivatives, N-(9-carboxynonyl)- and N-(11-carboxyundecyl)-deoxynojirimycin, were used for the affinity purification of acid beta-glucosidase (beta-Glc) from normal and type-1 Ashkenazi Jewish Gaucher disease (AJGD) sources. The capacities of these nondegradable inhibitor supports were 0.5 and 0.75 mg of normal beta-Glc/ml of settled gel, respectively. The purified normal enzyme (14-18% yield) had a specific activity of 1.6 X 10(6) nmol/h/mg protein and was homogeneous as evidenced by a single protein species of Mr = 67,000 on sodium dodecylsulfate-polyacrylamide gel electrophoresis and reverse phase high-performance liquid chromatography (HPLC). Microsequencing demonstrated a single N terminus, and the sequence of the first 22 N-terminal amino acids was colinear with that predicted from the beta-Glc cDNA. Amino acid composition analyses of beta-Glc revealed a high content (35%) of hydrophobic amino acids. The N-decyl-deoxynojirimycin support facilitated the purification of the residual enzyme from type-1 AJGD spleen to about 7,500-fold in four steps with a yield of about 11%. These new affinity supports provided improved stability, capacity and/or specificity compared to other affinity or HPLC methods for purifying this lysosomal glycosidase.

CONTROLLED TERM: Check Tags: Comparative Study; Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
1-Deoxynojirimycin
Amino Acid Sequence
Chromatography, Affinity
Chromatography, High Pressure Liquid
Electrophoresis, Polyacrylamide Gel
***Gaucher Disease: EN, enzymology**
Glucosamine: AA, analogs & derivatives
*Glucosidases: IP, isolation & purification
Peptide Fragments
*Placenta: EN, enzymology
Pregnancy
*Spleen: EN, enzymology
*beta-Glucosidase: IP, isolation & purification
CAS REGISTRY NO.: 19130-96-2 (1-Deoxynojirimycin); 3416-24-8 (Glucosamine)
CHEMICAL NAME: 0 (Peptide Fragments); EC 3.2.1.- (Glucosidases); EC 3.2.1.21 (beta-Glucosidase)

L99 ANSWER 20 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002169631 EMBASE
TITLE: New prospects for the treatment of lysosomal storage diseases.
AUTHOR: Schiffmann R.; Brady R.O.
CORPORATE SOURCE: Dr. R. Schiffmann, National Institutes of Health, Building 10, 9000 Rockville Pike, Bethesda, MD 20892-1260, United

States. RS4e@nih.gov
SOURCE: Drugs, (2002) 62/5 (733-742).
Refs: 65
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Although individually rare, lysosomal storage disorders constitute a significant burden on society. To date, enzyme replacement therapy (ERT) has been the most successful therapeutic approach for lysosomal storage disorders. ERT reverses systemic manifestations of Gaucher disease but does not effectively treat the neurological complications. Recently, ERT produced a reduction of severe neuropathic pain, stabilisation of renal disease, and improved vascular function and structure in short-term, placebo-controlled trials in patients with Fabry's disease. Long-term studies are necessary to evaluate the full potential of ERT in this disease. In patients with Pompe disease, a fatal cardiac and skeletal muscle disorder, ERT improved cardiac function and structure, and increased overall muscle strength. It has already increased survival in a small number of affected infants. ERT also decreased liver and spleen size, joint mobility and quality of life in patients with mucopolysaccharidosis type I, but when the therapeutic protein is administered intravenously, it is unlikely to modify the neurological outcome in this or in other similar disorders. Bone marrow transplantation continues to be effective in Gaucher disease, in some forms of mucopolysaccharidosis and in mild forms of Krabbe disease, but it has high morbidity and mortality that limits its use in lysosomal storage disorders. Drugs that slow the rate of formation of accumulating glycolipids are being developed and one of them, OGT-918 (N-butyldeoxynojirimycin), is showing promise in patients with Gaucher disease. Gene therapy for lysosomal storage disorders holds promise as a replacement for the other therapies described here but requires much more development before clinical efficacy trials.

CONTROLLED TERM: Medical Descriptors:
*lysosome storage disease: DT, drug therapy
*lysosome storage disease: TH, therapy
enzyme replacement
Gaucher disease: DT, drug therapy
Gaucher disease: TH, therapy
Fabry disease: DT, drug therapy
glycogen storage disease type 2: DT, drug therapy
mucopolysaccharidosis: DT, drug therapy
mucopolysaccharidosis: TH, therapy
neurological complication: CO, complication
drug effect
bone marrow transplantation
globoid cell leukodystrophy: TH, therapy
lipogenesis
gene therapy
drug hypersensitivity: SI, side effect
human
nonhuman
clinical trial
review
Drug Descriptors:
enzyme: AE, adverse drug reaction
enzyme: CT, clinical trial

enzyme: AD, drug administration
enzyme: CB, drug combination
enzyme: DO, drug dose
enzyme: DT, drug therapy
enzyme: PK, pharmacokinetics
enzyme: IV, intravenous drug administration
n butyldeoxynojirimycin: CT, clinical trial
n butyldeoxynojirimycin: DO, drug dose
n butyldeoxynojirimycin: DT, drug therapy
bisphosphonic acid derivative: CT, clinical trial
bisphosphonic acid derivative: CB, drug combination
bisphosphonic acid derivative: DT, drug therapy
alendronic acid: CT, clinical trial
alendronic acid: CB, drug combination
alendronic acid: DT, drug therapy
alpha galactosidase: AE, adverse drug reaction
alpha galactosidase: CT, clinical trial
alpha galactosidase: AD, drug administration
alpha galactosidase: DO, drug dose
alpha galactosidase: DT, drug therapy
alpha galactosidase: PK, pharmacokinetics
alpha galactosidase: IV, intravenous drug administration
alpha glucosidase: DO, drug dose
alpha glucosidase: DT, drug therapy
levo iduronidase: AE, adverse drug reaction
levo iduronidase: CT, clinical trial
levo iduronidase: DO, drug dose
levo iduronidase: DT, drug therapy
ogt 918

CAS REGISTRY NO.: (n butyldeoxynojirimycin) **72599-27-0**; (alendronic acid) 66376-36-1; (alpha galactosidase) 9023-01-2; (alpha glucosidase) 9001-42-7
CHEMICAL NAME: Ogt 918

L99 ANSWER 21 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002245071 EMBASE
TITLE: Low-dose N-butyldeoxynojirimycin (OGT 918) for type I Gaucher disease.
AUTHOR: Heitner R.; Elstein D.; Aerts J.; Van Weely S.; Zimran A.
CORPORATE SOURCE: D. Elstein, Gaucher Clinic, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel. gaucher@szmc.org.il
SOURCE: Blood Cells, Molecules, and Diseases, (2002) 28/2 (127-133).
Refs: 4
ISSN: 1079-9796 CODEN: BCMDFX
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
The objective of this study was to evaluate the efficacy and safety of low-dose substrate balance therapy with OGT 918 for the treatment of adults with Gaucher disease. Eighteen patients with Gaucher disease from two centers were enrolled in an open-label 6-month study of OGT 918, 50 mg taken three times daily (TID), followed by an optional extended-use phase. Changes in liver and spleen volume at 6 and 12 months, as well as routine hematological and biochemical parameters on a monthly basis, were evaluated. During the extension, dosage was increased to 100 mg TID in patients in one center to improve the response. Seventeen

patients completed 6 months; of 16 patients in the extension phase, 13 were evaluable at 12 months. Percentage changes in liver (-5.9%, P = 0.007) and spleen (-4.5%, P = 0.025) volumes and in chitotriosidase levels (-4.6%, P =0.039) at 6 months were commensurately lower than those reported previously in an open-label trial using 100 mg TID; hemoglobin and platelet counts were not boosted. At 12 months there were further mean decreases from baseline in liver volume (-6.2%, P = 0.037), spleen volume (-10.1%, P < 0.05), and chitotriosidase levels (-15.3%, P < 0.05) as well as mean changes of -2.27 and +14.7% in hemoglobin and platelet concentrations, respectively. There were no serious adverse effects throughout the 6-month study period; common side effects were diarrhea (94%) and weight loss (67%), comparable to the incidence in the original trial. We conclude that OGT 918 was safe and effective at 50 mg TID, but shows dose dependency in ameliorating parameters of Gaucher disease relative to the results noted in the seminal trial; there was no improvement in the rate of hematological response and no reduction in side effects. Results from the extension wherein some patients were dose increased suggest that 100 mg TID should be the preferred starting regimen for patients with symptomatic type I Gaucher disease.

CONTROLLED TERM: Medical Descriptors:
***Gaucher disease: DT, drug therapy**
dose response
drug efficacy
drug safety
liver weight
treatment outcome
spleen weight
thrombocyte count
diarrhea: SI, side effect
weight reduction
drug half life
abdominal pain: SI, side effect
flatulence: SI, side effect
headache: SI, side effect
tremor: SI, side effect
influenza: SI, side effect
disease classification
human
male
female
clinical article
clinical trial
phase 1 clinical trial
phase 2 clinical trial
adult
article
priority journal
Drug Descriptors:
*n butyldeoxynojirimycin: AE, adverse drug reaction
*n butyldeoxynojirimycin: CT, clinical trial
*n butyldeoxynojirimycin: DO, drug dose
*n butyldeoxynojirimycin: DT, drug therapy
*n butyldeoxynojirimycin: PK, pharmacokinetics
*n butyldeoxynojirimycin: PD, pharmacology
*n butyldeoxynojirimycin: PO, oral drug administration
enzyme: EC, endogenous compound
chitotriosidase: EC, endogenous compound
hemoglobin: EC, endogenous compound
unclassified drug
ogt 918

CAS REGISTRY NO.: (n butyldeoxynojirimycin) **72599-27-0;**
(hemoglobin) 9008-02-0

CHEMICAL NAME: Ogt 918

L99 ANSWER 22 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002216463 EMBASE
TITLE: Novel treatment for neuronopathic lysosomal storage diseases-cell therapy/gene therapy.
AUTHOR: Eto Y.; Ohashi T.
CORPORATE SOURCE: Y. Eto, Department of Pediatrics, Tokyo Jikei Univ. School of Medicine, Institute for DNA Medicine, Nishishinbashi 3-25-8, Minato-ku, Tokyo, Japan. yosh@sepia.ocn.ne.jp
SOURCE: Current Molecular Medicine, (2002) 2/1 (83-89).
Refs: 96
ISSN: 1566-5240 CODEN: CMMUBP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Most lysosomal storage diseases (LSD) exhibit neurological symptoms and there has been limited success in their treatment. Innovative treatments employing novel therapy or gene therapy may offer the prospect of improvement. Recent attempts to treat the neurological forms of LSD include neural stem cell therapy, mesenchymal stem cell therapy, hematopoietic stem cell therapy and gene therapy. Additional approaches have included substrate deprivation/chaperone therapy for the treatment of LSD. This article reviews these new technologies, discusses recent progress, and suggests their possible application.

CONTROLLED TERM: Medical Descriptors:
***Gaucher disease: DT, drug therapy**
*Gaucher disease: SU, surgery
*Gaucher disease: TH, therapy
*lysosome storage disease: DT, drug therapy
*lysosome storage disease: SU, surgery
*lysosome storage disease: TH, therapy
adoptive immunotherapy
gene therapy
neurologic disease: DT, drug therapy
neurologic disease: SU, surgery
neurologic disease: TH, therapy
symptomatology
treatment outcome
bone marrow transplantation
enzyme replacement
viral gene delivery system
adenovirus vector
retrovirus vector
lentivirus vector
hematopoietic stem cell transplantation
enzyme therapy
Niemann Pick disease: DT, drug therapy
Hunter syndrome: DT, drug therapy
Maroteaux Lamy syndrome: DT, drug therapy
chronic diarrhea: SI, side effect
human
nonhuman
mouse
clinical trial

animal model
controlled study
article
Drug Descriptors:
chaperone: EC, endogenous compound
carbamazepine: DT, drug therapy
normephenytoin: DT, drug therapy
cyclosporin: DT, drug therapy
somatomedin B receptor: EC, endogenous compound
alpha galactosidase: EC, endogenous compound
galactosylceramidase: DT, drug therapy
galactosylceramidase: EC, endogenous compound
galactosylceramidase: PR, pharmaceutics
galactosylceramidase: IV, intravenous drug administration
n butyldeoxynojirimycin: AE, adverse drug reaction
n butyldeoxynojirimycin: CT, clinical trial
n butyldeoxynojirimycin: DT, drug therapy
n butyldeoxynojirimycin: PD, pharmacology
pyrrolidine derivative
enzyme inhibitor: DT, drug therapy
enzyme inhibitor: PD, pharmacology
ganglioside GM2: EC, endogenous compound
beta glucuronidase: DT, drug therapy
beta glucuronidase: PR, pharmaceutics
beta glucuronidase: IV, intravenous drug administration
complementary DNA
CAS REGISTRY NO.: (carbamazepine) 298-46-4, 8047-84-5; (normephenytoin) 631-07-2; (cyclosporin) 79217-60-0; (alpha galactosidase) 9023-01-2; (galactosylceramidase) 9027-89-8; (n butyldeoxynojirimycin) **72599-27-0**; (ganglioside GM2) 19600-01-2; (beta glucuronidase) 9001-45-0

L99 ANSWER 23 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001087279 EMBASE
TITLE: Substrate reduction therapy for glycosphingolipid storage disorders.
AUTHOR: Lachmann R.H.; Platt F.M.
CORPORATE SOURCE: R.H. Lachmann, Department of Medicine, University of Cambridge, Addenbrooke's Hospitals, Hills Road, Cambridge CB2 2QQ, United Kingdom. rh120@cam.ac.uk
SOURCE: Expert Opinion on Investigational Drugs, (2001) 10/3 (455-466).
Refs: 59
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Substrate reduction therapy is a novel approach to treating glycosphingolipid (GSL) lysosomal storage disorders. These diseases are caused by mutations in the genes coding for enzymes involved in GSL catabolism and are characterised by the accumulation of GSL substrates within the lysosomes of cells. The aim of substrate reduction therapy is to inhibit the rate of synthesis of GSLs to levels where the residual activity of the mutant catabolic enzyme is sufficient to prevent pathological storage. In this review we discuss the development of N-butyldeoxynojirimycin (NB-DNJ), an imino sugar that inhibits the ceramide-specific glucosyltransferase which catalyses the first committed step of GSL synthesis. This agent has been shown to slow accumulation of stored

glycolipid in an in vitro model of Gaucher's disease and in knockout mouse models of Tay-Sachs and Sandhoff diseases. Furthermore, administration of NB-DNJ to Sandhoff mice delays the onset of neurological disease and also slows its progression. We discuss safety and efficacy data from the clinical trial of substrate reduction with NB-DNJ which has been undertaken in patients with Type 1 Gaucher's disease. This trial provides a proof-of-principle for the use of this approach in a wide range of GSL lysosomal storage diseases.

CONTROLLED TERM: Medical Descriptors:
*Fabry disease: DT, drug therapy
biosynthesis
enzyme inhibition
drug mechanism
in vitro study
Gaucher disease: DT, drug therapy
knockout mouse
Tay Sachs disease: DT, drug therapy
Sandhoff disease: DT, drug therapy
drug structure
drug blood level
drug safety
gastrointestinal tract
target organ
diarrhea: SI, side effect
flatulence: SI, side effect
nausea: SI, side effect
weight reduction
paresthesia: SI, side effect
drug efficacy
hepatosplenomegaly
human
nonhuman
mouse
clinical trial
animal experiment
animal model
controlled study
animal tissue
animal cell
review
Drug Descriptors:
*glycosphingolipid: EC, endogenous compound
*n butyldeoxynojirimycin: AE, adverse drug reaction
*n butyldeoxynojirimycin: CT, clinical trial
*n butyldeoxynojirimycin: AN, drug analysis
*n butyldeoxynojirimycin: CR, drug concentration
*n butyldeoxynojirimycin: DO, drug dose
*n butyldeoxynojirimycin: DT, drug therapy
*n butyldeoxynojirimycin: PD, pharmacology
*n butyldeoxynojirimycin: PO, oral drug administration
ceramide glucosyltransferase: EC, endogenous compound
glycolipid: EC, endogenous compound
alglucerase: EC, endogenous compound
sphinganine: EC, endogenous compound
ceramide: EC, endogenous compound
galactosylceramide: EC, endogenous compound
sphingomyelin: EC, endogenous compound
lactosylceramide: EC, endogenous compound
palmitoyl coenzyme A: EC, endogenous compound
glucosyltransferase: EC, endogenous compound
uridine diphosphate: EC, endogenous compound
glucose: EC, endogenous compound
globotriaosylceramide: EC, endogenous compound

ganglioside GM2: EC, endogenous compound
ganglioside GM1: EC, endogenous compound
glucosylceramidase: EC, endogenous compound
alpha galactosidase: EC, endogenous compound
beta n acetylhexosaminidase A: EC, endogenous compound
ogt 918

CAS REGISTRY NO.: (n butyldeoxynojirimycin) **72599-27-0**; (ceramide glucosyltransferase) 37237-44-8; (sphinganine) 764-22-7; (galactosylceramide) 85305-88-0; (sphingomyelin) 85187-10-6; (lactosylceramide) 4682-48-8; (palmitoyl coenzyme A) 1763-10-6; (glucosyltransferase) 9031-48-5; (uridine diphosphate) 58-98-0; (glucose) 50-99-7, 84778-64-3; (globotriaosylceramide) 71965-57-6; (ganglioside GM2) 19600-01-2; (ganglioside GM1) 37758-47-7; (glucosylceramidase) 37228-64-1; (alpha galactosidase) 9023-01-2

CHEMICAL NAME: Ogt 918

L99 ANSWER 24 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000419619 EMBASE

TITLE: Niemann-Pick type C: A disorder of cellular cholesterol trafficking.

AUTHOR: Ory D.S.

CORPORATE SOURCE: D.S. Ory, Department of Internal Medicine, Washington University, School of Medicine, 660 S Euclid Avenue, St Louis, MO 63110-1093, United States. dory@imgate.wustl.edu

SOURCE: Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids, (15 Dec 2000) 1529/1-3 (331-339).
Refs: 57
ISSN: 1388-1981 CODEN: BBMLFG

PUBLISHER IDENT.: S 1388-1981(00)00158-X

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT:
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery

LANGUAGE: English

CONTROLLED TERM: Medical Descriptors:
*Niemann Pick disease: ET, etiology
*cholesterol transport
clinical feature
cell function
homeostasis
protein structure, function and variability
autosomal recessive disorder: ET, etiology
phenotype
degenerative disease: ET, etiology
Gaucher disease: DT, drug therapy
niemann pick disease type c: ET, etiology
human
nonhuman
mouse
animal model
clinical trial
review
priority journal
Drug Descriptors:
*cholesterol: EC, endogenous compound
sterol: EC, endogenous compound
glycolipid: EC, endogenous compound

glycosphingolipid: EC, endogenous compound
n butyldeoxynojirimycin: PD, pharmacology
n butyldeoxynojirimycin: DT, drug therapy
n butyldeoxynojirimycin: CT, clinical trial
CAS REGISTRY NO.: (cholesterol) 57-88-5; (n butyldeoxynojirimycin) **72599-27-0**

L99 ANSWER 25 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001403483 EMBASE
TITLE: Remaining problems in the management of patients with Gaucher disease.
AUTHOR: Erikson A.
CORPORATE SOURCE: A. Erikson, Department of Pediatrics, Umea University Hospital, 901 85 Umea, Sweden. anders.erikson.us@vll.se
SOURCE: Journal of Inherited Metabolic Disease, (2001) 24/SUPPL. 2 (122-126).
Refs: 28
ISSN: 0141-8955 CODEN: JIMDDP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
029 Clinical Biochemistry
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
The history of treatment of Gaucher disease started with splenectomy and continued with bone marrow transplantation, before the recent introduction of enzyme replacement therapy. Although the latter has revolutionized the prognosis of patients, many questions remain to be answered and clinical management problems resolved. These include how to monitor enzyme replacement to determine the optimal dosage, how to treat mild disease, whether intermittent treatment is an option, and the causes of the neurological signs and how to treat them. The pulmonary hypertension problem has also not been resolved, and we need to determine how to treat and monitor bone disease. In addition, the future role of substrate deprivation needs to be determined, and further research is required before gene therapy becomes a potential clinical option. The high cost of enzyme replacement treatment for Gaucher disease remains an important issue.

CONTROLLED TERM: Medical Descriptors:
***Gaucher disease: DT, drug therapy**
*Gaucher disease: SU, surgery
*Gaucher disease: TH, therapy
history
splenectomy
bone marrow transplantation
enzyme replacement
prognosis
patient monitoring
dose response
disease severity
neurologic disease: DT, drug therapy
pulmonary hypertension
bone disease: DT, drug therapy
enzyme substrate
gene therapy
drug mechanism
diarrhea: SI, side effect
drug cost

human
controlled study
article
Drug Descriptors:
enzyme: DO, drug dose
enzyme: DT, drug therapy
enzyme: PE, pharmacoeconomics
enzyme: PD, pharmacology
alglucerase: DT, drug therapy
alglucerase: PD, pharmacology
n butyldeoxynojirimycin: AE, adverse drug reaction
n butyldeoxynojirimycin: DT, drug therapy
n butyldeoxynojirimycin: PD, pharmacology
n butyldeoxynojirimycin: PO, oral drug administration
calcium: DT, drug therapy
vitamin D: DT, drug therapy
bisphosphonic acid derivative: DT, drug therapy
ogt 918

CAS REGISTRY NO.: (n butyldeoxynojirimycin) **72599-27-0**; (calcium) 7440-70-2
CHEMICAL NAME: Ogt 918

L99 ANSWER 26 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001054594 EMBASE
TITLE: Stemming the tide: Glycosphingolipid synthesis inhibitors as therapy for storage diseases.
AUTHOR: Tifft C.J.; Proia R.I.
CORPORATE SOURCE: R.L. Proia, National Institutes of Health, Gen. of Dev. and Disease Branch, National Institutes of Diabetes, Building 10, Bethesda, MD 20892, United States
SOURCE: Glycobiology, (2000) 10/12 (1249-1258).
Refs: 63
ISSN: 0959-6658 CODEN: GLYCE3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Glycosphingolipids (GSLs) are plasma membrane components of every eukaryotic cell. They are composed of a hydrophobic ceramide moiety linked to a glycan chain of variable length and structure. Once thought to be relatively inert, GSLs have now been implicated in a variety of biological processes. Recent studies of animals rendered genetically deficient in various classes of GSLs have demonstrated that these molecules are important for embryonic differentiation and development as well as central nervous system function. A family of extremely severe disease is caused by inherited defects in the lysosomal degradation pathway of GSLs. In many of these disorders GSLs accumulate in cells, particularly neurons, causing neurodegeneration and a shortened life span. No effective treatment exists for most of these diseases and little is understood about the mechanisms of pathogenesis. This review will discuss the development of a new approach to the treatment of GSL storage disorders that targets the major synthesis pathway of GSLs to stem their cellular accumulation.

CONTROLLED TERM: Medical Descriptors:
*storage disease: DT, drug therapy
cell membrane
eukaryotic cell
chemical composition
hydrophobicity

chemical structure
genetics
embryo development
central nervous system
disease severity
inheritance
lysosome storage disease
nerve degeneration: ET, etiology
lifespan
pathogenesis
biosynthesis
drug structure
diarrhea: SI, side effect
neuropathy: SI, side effect
weight reduction
drug metabolism
Tay Sachs disease: DT, drug therapy
Gaucher disease: DT, drug therapy
Fabry disease: DT, drug therapy
Sandhoff disease: DT, drug therapy
GM1 gangliosidosis: DT, drug therapy
Niemann Pick disease: DT, drug therapy
human
nonhuman
mouse
clinical trial
animal experiment
animal model
controlled study
review
priority journal
Drug Descriptors:
*glycosphingolipid synthesis inhibitor: AE, adverse drug reaction
*glycosphingolipid synthesis inhibitor: CT, clinical trial
*glycosphingolipid synthesis inhibitor: AN, drug analysis
*glycosphingolipid synthesis inhibitor: DT, drug therapy
*glycosphingolipid synthesis inhibitor: PK, pharmacokinetics
*glycosphingolipid synthesis inhibitor: PD, pharmacology
*glycosphingolipid synthesis inhibitor: PO, oral drug administration
*blocking agent: AE, adverse drug reaction
*blocking agent: CT, clinical trial
*blocking agent: AN, drug analysis
*blocking agent: PK, pharmacokinetics
*blocking agent: PD, pharmacology
*blocking agent: PO, oral drug administration
*glycosphingolipid: EC, endogenous compound
ceramide: EC, endogenous compound
glycan: EC, endogenous compound
n butyldeoxygalactonojirimycin: AE, adverse drug reaction
n butyldeoxygalactonojirimycin: AN, drug analysis
n butyldeoxygalactonojirimycin: DT, drug therapy
n butyldeoxygalactonojirimycin: PK, pharmacokinetics
n butyldeoxygalactonojirimycin: PD, pharmacology
n butyldeoxynojirimycin: AE, adverse drug reaction
n butyldeoxynojirimycin: CT, clinical trial
n butyldeoxynojirimycin: AN, drug analysis
n butyldeoxynojirimycin: DT, drug therapy
n butyldeoxynojirimycin: PK, pharmacokinetics
n butyldeoxynojirimycin: PD, pharmacology
n butyldeoxynojirimycin: PO, oral drug administration

dextro threo 1 (3',4' ethylenedioxy)phenyl 2 palmitoylamino 3 pyrrolidino 1 propanol: AE, adverse drug reaction
dextro threo 1 (3',4' ethylenedioxy)phenyl 2 palmitoylamino 3 pyrrolidino 1 propanol: CT, clinical trial
dextro threo 1 (3',4' ethylenedioxy)phenyl 2 palmitoylamino 3 pyrrolidino 1 propanol: AN, drug analysis
dextro threo 1 (3',4' ethylenedioxy)phenyl 2 palmitoylamino 3 pyrrolidino 1 propanol: DT, drug therapy
dextro threo 1 (3',4' ethylenedioxy)phenyl 2 palmitoylamino 3 pyrrolidino 1 propanol: PK, pharmacokinetics
dextro threo 1 (3',4' ethylenedioxy)phenyl 2 palmitoylamino 3 pyrrolidino 1 propanol: PD, pharmacology
dextro 4' hydroxy 1 phenyl 2 palmitoylamino 2 pyrrolidino 1 propanol: AE, adverse drug reaction
dextro 4' hydroxy 1 phenyl 2 palmitoylamino 2 pyrrolidino 1 propanol: CT, clinical trial
dextro 4' hydroxy 1 phenyl 2 palmitoylamino 2 pyrrolidino 1 propanol: AN, drug analysis
dextro 4' hydroxy 1 phenyl 2 palmitoylamino 2 pyrrolidino 1 propanol: DT, drug therapy
dextro 4' hydroxy 1 phenyl 2 palmitoylamino 2 pyrrolidino 1 propanol: PK, pharmacokinetics
dextro 4' hydroxy 1 phenyl 2 palmitoylamino 2 pyrrolidino 1 propanol: PD, pharmacology
dextro threo 1 phenyl 2 decanoylamino 3 morpholino 1 propanol: AE, adverse drug reaction
dextro threo 1 phenyl 2 decanoylamino 3 morpholino 1 propanol: CT, clinical trial
dextro threo 1 phenyl 2 decanoylamino 3 morpholino 1 propanol: AN, drug analysis
dextro threo 1 phenyl 2 decanoylamino 3 morpholino 1 propanol: DT, drug therapy
dextro threo 1 phenyl 2 decanoylamino 3 morpholino 1 propanol: PK, pharmacokinetics
dextro threo 1 phenyl 2 decanoylamino 3 morpholino 1 propanol: PD, pharmacology
propanol
beta n acetylhexosaminidase A: EC, endogenous compound
beta n acetylhexosaminidase B: EC, endogenous compound
beta glucosidase: EC, endogenous compound
beta galactosidase: EC, endogenous compound
ganglioside GM2: EC, endogenous compound
ganglioside GA2: EC, endogenous compound
ganglioside: EC, endogenous compound
oligosaccharide: EC, endogenous compound
galactosylceramide: EC, endogenous compound
globotriaosylceramide: EC, endogenous compound
galabiosylceramide: EC, endogenous compound
ceramide derivative: EC, endogenous compound
keratan sulfate: EC, endogenous compound
sphingomyelin: EC, endogenous compound
cholesterol: EC, endogenous compound
ganglioside GM3: EC, endogenous compound
lactosylceramide: EC, endogenous compound
sphingosine: EC, endogenous compound
sulfatide: EC, endogenous compound
unindexed drug
unclassified drug

CAS REGISTRY NO.: (n butyldeoxynojirimycin) **72599-27-0**; (propanol) 62309-51-7, 71-23-8; (beta glucosidase) 51683-43-3, 9001-22-3; (ganglioside GM2) 19600-01-2; (galactosylceramide) 85305-88-0; (globotriaosylceramide) 71965-57-6; (keratan sulfate) 69992-87-6, 9056-36-4;

(sphingomyelin) 85187-10-6; (cholesterol) 57-88-5; (ganglioside GM3) 54827-14-4; (lactosylceramide) 4682-48-8; (sphingosine) 123-78-4

L99 ANSWER 27 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001012300 EMBASE
TITLE: Treating glucosphingolipid disorders by chemotherapy: Use of approved drugs and over-the-counter remedies.
AUTHOR: Radin N.S.
CORPORATE SOURCE: N.S. Radin, 350 Sharon Park Dr., Menlo Park, CA 94025, United States. Glyconorm@aol.com
SOURCE: Journal of Inherited Metabolic Disease, (2000) 23/8 (767-777).
Refs: 40
ISSN: 0141-8955 CODEN: JIMDDP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
The accumulation of a glucosphingolipid (GSL) in individuals lacking an adequate level of hydrolase activity could be minimized by chemotherapeutic measures that slow the formation of the GSL and stimulate the defective hydrolase. By achieving a balance in the rates of formation and breakdown, one should be able to alleviate the symptoms of excess storage and achieve a satisfactory accommodation. While several drugs seem to be specifically suitable for this purpose, only one of these has been approved for human use. However, less effective drugs and over-the-counter substances are available for human use and may prove satisfactory for a few years until better ones are made available. The proposed materials and the evidence behind the recommendations are presented in this paper.

CONTROLLED TERM: Medical Descriptors:
*lipidosis: DT, drug therapy
*lipidosis: ET, etiology
Gaucher disease: DT, drug therapy
Fabry disease: DT, drug therapy
Fabry disease: ET, etiology
Tay Sachs disease: DT, drug therapy
Tay Sachs disease: ET, etiology
Sandhoff disease: DT, drug therapy
Sandhoff disease: ET, etiology
fucosidosis: DT, drug therapy
fucosidosis: ET, etiology
GM1 gangliosidosis: DT, drug therapy
GM1 gangliosidosis: ET, etiology
lipid storage
enzyme deficiency: ET, etiology
pathogenesis
drug targeting
drug approval
enzyme activation
enzyme activity
drug effect
substitution therapy
diet supplementation
low fat diet
treatment planning
diarrhea: SI, side effect

peripheral neuropathy: SI, side effect
evidence based medicine
human
nonhuman
mouse
animal experiment
animal model
controlled study
article
Drug Descriptors:
*non prescription drug: DT, drug therapy
*glycosphingolipid: EC, endogenous compound
hydrolase: EC, endogenous compound
hemoglobin: EC, endogenous compound
glucosylceramide: EC, endogenous compound
ceramide: EC, endogenous compound
lactosylceramide: EC, endogenous compound
globotriaosylceramide: EC, endogenous compound
uridine diphosphate glucose: EC, endogenous compound
ceramide glucosyltransferase: EC, endogenous compound
alpha galactosidase: EC, endogenous compound
beta galactosidase: EC, endogenous compound
ceramide glucosyltransferase inhibitor: DT, drug therapy
ceramide glucosyltransferase inhibitor: PD, pharmacology
alglucerase: DT, drug therapy
alglucerase: PD, pharmacology
glucosidase: DT, drug therapy
glucosidase: PD, pharmacology
cycloserine: DT, drug therapy
cycloserine: PD, pharmacology
n butyldeoxynojirimycin: AE, adverse drug reaction
n butyldeoxynojirimycin: DO, drug dose
n butyldeoxynojirimycin: DT, drug therapy
n butyldeoxynojirimycin: PD, pharmacology
n butyldeoxynojirimycin: PO, oral drug administration
2 decanoylamino 3 morpholino 1 phenyl 1 propanol: DT, drug therapy
2 decanoylamino 3 morpholino 1 phenyl 1 propanol: BD, buccal drug administration
2 decanoylamino 3 morpholino 1 phenyl 1 propanol: IP, intraperitoneal drug administration
tamoxifen: AE, adverse drug reaction
tamoxifen: DT, drug therapy
tamoxifen: PD, pharmacology
verapamil: DT, drug therapy
verapamil: PD, pharmacology
doxorubicin: DT, drug therapy
doxorubicin: PD, pharmacology
mifepristone: DT, drug therapy
mifepristone: PD, pharmacology
retinol: CM, drug comparison
retinol: DT, drug therapy
retinol: PD, pharmacology
antioxidant: DT, drug therapy
antioxidant: PD, pharmacology
retinoic acid derivative: DT, drug therapy
retinoic acid derivative: PD, pharmacology
fenretinide: CM, drug comparison
fenretinide: DT, drug therapy
fenretinide: PD, pharmacology
glucose: EC, endogenous compound
acarbose: DT, drug therapy
acarbose: PD, pharmacology

glucocorticoid: PD, pharmacology
unindexed drug
CAS REGISTRY NO.: (hydrolase) 9027-41-2; (hemoglobin) 9008-02-0; (lactosylceramide) 4682-48-8; (globotriaosylceramide) 71965-57-6; (uridine diphosphate glucose) 133-89-1; (ceramide glucosyltransferase) 37237-44-8; (alpha galactosidase) 9023-01-2; (glucosidase) 9033-06-1; (cycloserine) 339-72-0, 68-39-3, 68-41-7; (n butyldeoxynojirimycin) **72599-27-0**; (2 decanoylamino 3 morpholino 1 phenyl 1 propanol) 109836-82-0, 73257-80-4; (tamoxifen) 10540-29-1; (verapamil) 152-11-4, 52-53-9; (doxorubicin) 23214-92-8, 25316-40-9; (mifepristone) 84371-65-3; (retinol) 68-26-8, 82445-97-4; (fenretinide) 65646-68-6, 75686-07-6; (glucose) 50-99-7, 84778-64-3; (acarbose) 56180-94-0
CHEMICAL NAME: Ru 486; Adriamycin; Ceredase

L99 ANSWER 28 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000196634 EMBASE
TITLE: Orphan drugs and orphan diseases.
AUTHOR: Campos-Castello J.; Ponsot G.; Feillet F.; Vidailhet M.; Maire I.
CORPORATE SOURCE: Dr. J. Campos-Castello, University Hospital San Carlos, Servicio de Neuropediatria, Martin Lagos s/n, 28040 Madrid, Spain. jcampos@hcsc.insalud.es
SOURCE: European Journal of Paediatric Neurology, (2000) 4/3 (141-149).
Refs: 25
ISSN: 1090-3798 CODEN: EJPNFO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: English

CONTROLLED TERM: Medical Descriptors:
*urea cycle
*enzyme deficiency: CN, congenital disorder
*enzyme deficiency: DT, drug therapy
*enzyme deficiency: TH, therapy
*lysosome storage disease: DT, drug therapy
*lysosome storage disease: SU, surgery
*lysosome storage disease: TH, therapy
nitrogen balance
protein restriction
pregnancy
bone marrow transplantation
gene therapy
drug manufacture
Gaucher disease: CN, congenital disorder
Gaucher disease: DT, drug therapy
Fabry disease: CN, congenital disorder
Niemann Pick disease: CN, congenital disorder
inborn error of metabolism: CN, congenital disorder
glycogen storage disease type 2: CN, congenital disorder
Hurler syndrome: CN, congenital disorder
human
nonhuman
mouse
article
priority journal
Drug Descriptors:

*orphan drug
*ornithine carbamoyltransferase: EC, endogenous compound
*argininosuccinate synthase: EC, endogenous compound
*argininosuccinate lyase: EC, endogenous compound
*benzoic acid: DT, drug therapy
*mercaptamine: DT, drug therapy
urea
nitrogen
glycine
glutamine
arylbutyric acid derivative
phenylacetic acid: DT, drug therapy
arginase: EC, endogenous compound
glutamate acetyltransferase: EC, endogenous compound
somatomedin B receptor
alglucerase: DT, drug therapy
alpha galactosidase: EC, endogenous compound
sphingomyelin phosphodiesterase: EC, endogenous compound
levo iduronidase: EC, endogenous compound
glucan 1,4 alpha glucosidase: EC, endogenous compound
n butyldeoxynojirimycin
uridine diphosphate glucose

CAS REGISTRY NO.: (ornithine carbamoyltransferase) 9001-69-8; (argininosuccinate synthase) 9023-58-9; (argininosuccinate lyase) 9027-34-3; (benzoic acid) 532-32-1, 582-25-2, 65-85-0, 766-76-7; (mercaptamine) 156-57-0, 60-23-1; (urea) 57-13-6; (nitrogen) 7727-37-9; (glycine) 56-40-6, 6000-43-7, 6000-44-8; (glutamine) 56-85-9, 6899-04-3; (phenylacetic acid) 103-82-2; (arginase) 9000-96-8; (glutamate acetyltransferase) 37257-14-0; (alpha galactosidase) 9023-01-2; (sphingomyelin phosphodiesterase) 9031-54-3; (glucan 1,4 alpha glucosidase) 9032-08-0; (n butyldeoxynojirimycin) **72599-27-0**; (uridine diphosphate glucose) 133-89-1

L99 ANSWER 29 OF 30 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998345389 EMBASE
TITLE: New therapeutic prospects for the glycosphingolipid lysosomal storage diseases.
AUTHOR: Platt F.M.; Butters T.D.
CORPORATE SOURCE: Dr. F.M. Platt, Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, United Kingdom. Fran@oxglua.glycob.ox.ac.uk
SOURCE: Biochemical Pharmacology, (1998) 56/4 (421-430).
Refs: 50
ISSN: 0006-2952 CODEN: BCPCA6
PUBLISHER IDENT.: S 0006-2952(98)00115-4
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
The glycosphingolipid (GSL) lysosomal storage diseases result from mutations in the genes that encode the enzymes required for glycosphingolipid catabolism within lysosomes. They are relatively rare diseases, but are frequently severe in terms of their pathology. Many involve progressive neurodegeneration, and in the most severe forms result in death in early infancy. The therapeutic options for treating these diseases are limited, and for the majority of these disorders there are currently no therapies available. To date, most research

has focused on correcting the genetic lesion by gene therapy or by augmenting the enzyme activity deficient in these patients by introducing fully functional enzyme. This can be achieved by bone marrow transplantation or intravenous infusion of purified or recombinant enzyme (enzyme replacement). Gene therapy and enzyme replacement therapy are disease specific, and pharmacological approaches for the treatment of these disorders have not been fully explored. In this commentary, the problems associated with disease therapy are discussed, and a pharmacological agent (N-butyldeoxynojirimycin) is presented for the potential generic treatment of this family of disorders. Successful prevention of glycosphingolipid storage in a mouse model of Tay-Sachs disease suggests that this strategy merits clinical evaluation. BIOCHEM PHARMACOL 56;4:421-430, 1998. (C) 1998 Elsevier Science Inc.

CONTROLLED TERM: Medical Descriptors:
*lysosome storage disease: TH, therapy
*lysosome storage disease: ET, etiology
*lysosome storage disease: DT, drug therapy
***gaucher disease: DT, drug therapy**
*gaucher disease: DI, diagnosis
*tay sachs disease: DT, drug therapy
*tay sachs disease: DI, diagnosis
gene mutation
drug metabolism
gene therapy
enzyme replacement
bone marrow transplantation
enzyme deficiency
genotype
enzyme assay
in vitro study
model
macrophage
human
nonhuman
mouse
animal cell
review
priority journal
Drug Descriptors:
*glycosphingolipid: EC, endogenous compound
beta galactosidase: EC, endogenous compound
alpha galactosidase: EC, endogenous compound
beta n acetylhexosaminidase: EC, endogenous compound
alpha levo fucosidase: EC, endogenous compound
arylsulfatase: EC, endogenous compound
enzyme inhibitor: DT, drug therapy
glucosidase: EC, endogenous compound
aminosugar: DT, drug therapy
n butyldeoxynojirimycin: DT, drug therapy

CAS REGISTRY NO.: (alpha galactosidase) 9023-01-2; (beta n acetylhexosaminidase) 37211-57-7, 9027-52-5; (alpha levo fucosidase) 9037-65-4; (arylsulfatase) 9016-17-5; (glucosidase) 9033-06-1; (n butyldeoxynojirimycin) **72599-27-0**

L99 ANSWER 30 OF 30 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-171538 [22] WPIDS
DOC. NO. CPI: C2002-052997
TITLE: Use of a combination of enzyme replacement therapy, gene therapy and small molecule therapy for treating lysosomal storage disease e.g. Fabry disease.
DERWENT CLASS: B03 D16
INVENTOR(S): CHENG, S H; MEEKER, D

PATENT ASSIGNEE(S): (GENZ) GENZYME CORP; (CHEN-I) CHENG S H; (MEEK-I) MEEKER D
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001097829	A2	20011227	(200222)*	EN	45	A61K038-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW						
AU 2001069923	A	20020102	(200230)			A61K038-00
US 2002095135	A1	20020718	(200254)			A61M031-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001097829	A2	WO 2001-US19579	20010619
AU 2001069923	A	AU 2001-69923	20010619
US 2002095135	A1 Provisional	US 2000-212377P	20000619
		US 2001-884526	20010619

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001069923	A Based on	WO 200197829

PRIORITY APPLN. INFO: US 2000-212377P 20000619; US 2001-884526 20010619
INT. PATENT CLASSIF.:
MAIN: A61K038-00; A61M031-00
BASIC ABSTRACT:
WO 200197829 A UPAB: 20020409
NOVELTY - Treatment of Fabry disease involves administering a combination therapy selected from at least two of an enzyme replacement therapy, gene therapy and small molecule therapy.
ACTIVITY - Nephrotropic.
MECHANISM OF ACTION - Gene Therapy; Enzyme replacement therapy; Small molecule therapy.
Fabry mice were used to test the in vivo efficacy of combining enzyme replacement therapy (ET) with small molecule therapy (SMT) in a sequential treatment format. The study called for a single infusion of alpha -galactosidase A enzyme to reduce globotriaosyl-ceramide (GB3) levels to a baseline level in Fabry mouse liver. GB3 re-accumulation was then measured at four weeks in control mice receiving no SMT and in mice receiving various small molecules (vehicle) at various doses. Two weeks after GB3 levels were reduced to baseline level of 0.1 micro g/g liver, a small molecule was administered by intraperitoneal injection. In the vehicle treated control mice, GB3 re-accumulated to 0.8 micro g/g liver tissue at the four week time point. By contrast, D-threo-1-(3', 4' -ethylenedioxy)phenyl-2-palmitoylamino-3-pyrrolidine-1-propanol (5 mg/kg) reduced GB3re-accumulation to less than 0.4 micro g/g liver tissue at 4 week time point. Similarly N-(5-adamantane-1-yl-methoxy)pentyl)-**deoxynojirimycin** (100 mg/kg) reduced GB3 re-accumulation to less than 0.3 micro g/g liver tissue at 4 week time point.
USE - For treating Fabry disease (claimed) and lysosomal storage disease (LSDS) e.g. **Gaucher**, Niemann-Pick, Farber, GMI-gangliosidosis, GM2-gangliosidosis (Sandhoff), Tay-Sachs, Krabbe,

Hurler-Scheie (MPS I), Hunter (MPS II), Sanfilippo (MPS III) Type A, Sanfilippo (MPS III) Type B, Sanfilippo (MPS III) Type C, Sanfilippo (MPS III) Type D, Marquio (MPS IV) Type A, Marquio (MPS IV) Type B, Maroteaux-Lamy (MPS VI), Sly (MPS VII), mucosulfatidosis, sialidoses, mucolipidosis II, mucolipidosis III, mucolipidosis IV, Fabry, Schindler, Pompe, sialic acid storage disease, fucosidosis, mannosidosis, aspartylglucosaminuria, Wolman, and neuronal ceroid lipofucsinoses.

ADVANTAGE - In Fabry if gene therapy does not reach the kidney wall enough for a clinical outcome, enzyme replacement therapy can be selectively targeted to the kidney. Other organs or disease loci such as bones and lung alveolar macrophages may not be well targeted by gene therapy, using enzyme replacement therapy however bones can be injected and lungs can be targeted with aerosols. Small molecule therapy is able to cross the blood-brain barrier (BBB) providing a powerful approach, when combined with gene and/or enzyme replacement therapy, for treating the disease having CNS manifestations. Substrate deprivation by small molecule therapy combined with enzyme replacement and/or gene therapy address the storage problem at separate and distinct intervention points which enhances clinical outcome. Gene therapy provides alpha -galactosudase A. The combination therapy produces a diminution in globotriaosylceramide.

Dwg.0/2

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-J; B04-B03C; B04-E01; B04-L01; B06-A02; B07-D03; B14-L06; B14-S03A; D05-C03; D05-H12A

=> fil reg
FILE 'REGISTRY' ENTERED AT 13:41:29 ON 15 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 OCT 2002 HIGHEST RN 461382-59-2
DICTIONARY FILE UPDATES: 14 OCT 2002 HIGHEST RN 461382-59-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s 72599-27-0

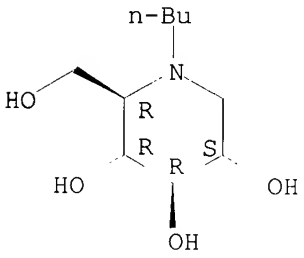
L100 1 72599-27-0
(72599-27-0/RN)

=> d ide

L100 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **72599-27-0** REGISTRY
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, (2R,3R,4R,5S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, [2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]-
OTHER NAMES:
CN Miglustat
CN N-Butyl-1-deoxynojirimycin
CN N-Butyldeoxynojirimycin
CN N-Butylmoranoline
CN NB-DNJ
CN OGT 918
CN SC 48334
FS STEREOSEARCH
DR 134282-77-2
MF C10 H21 N O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DRUGNL, DRUGUPDATES, EMBASE, IPA, MEDLINE, NAPRALERT, PHAR, PROMT, RTECS*, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

111 REFERENCES IN FILE CA (1962 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
111 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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=> fil capl; d que l41; d que l47; s (l41 or l47) not l36
FILE 'CAPLUS' ENTERED AT 13:42:02 ON 15 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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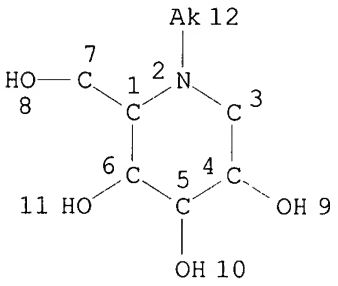
```


FILE COVERS 1907 - 15 Oct 2002 VOL 137 ISS 16
FILE LAST UPDATED: 14 Oct 2002 (20021014/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

L7 STR



NODE ATTRIBUTES:
CONNECT IS E1 RC AT 12
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

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L9          152 SEA FILE=REGISTRY SSS FUL L7
L10           1 SEA FILE=REGISTRY ABB=ON  GLUCOCEREBROSIDASE/CN
L28         224 SEA FILE=CAPLUS ABB=ON  L9
L29         698 SEA FILE=CAPLUS ABB=ON  L10
L35         899 SEA FILE=CAPLUS ABB=ON  GAUCHER?/OBI
L37         137 SEA FILE=CAPLUS ABB=ON  L29(L)(THU OR BAC OR PAC OR DMA OR
                PKT)/RL
L40           6 SEA FILE=CAPLUS ABB=ON  L28 AND L29 AND L35
L41           2 SEA FILE=CAPLUS ABB=ON  L37 AND L40
```

```
L10           1 SEA FILE=REGISTRY ABB=ON  GLUCOCEREBROSIDASE/CN
L29         698 SEA FILE=CAPLUS ABB=ON  L10
L35         899 SEA FILE=CAPLUS ABB=ON  GAUCHER?/OBI
L44         797 SEA FILE=CAPLUS ABB=ON  GAUCHER DISEASE+OLD/CT
L45          98 SEA FILE=CAPLUS ABB=ON  L29(L)THU/RL
L46          29 SEA FILE=CAPLUS ABB=ON  L45(L)L35 AND L44
L47           4 SEA FILE=CAPLUS ABB=ON  L46 AND REVIEW/DT


L101          5 (L41 OR L47) NOT L36
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previous printed

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=> fil medl; d que l56
FILE 'MEDLINE' ENTERED AT 13:42:32 ON 15 OCT 2002

 FILE LAST UPDATED: 12 OCT 2002 (20021012/UP).  FILE COVERS 1958 TO DATE.

 On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2002 vocabulary.  Enter HELP THESAURUS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.


L18         856 SEA FILE=MEDLINE ABB=ON  GLUCOSYLCERAMIDASE/CT
L26         264 SEA FILE=MEDLINE ABB=ON  L18(L)(TU OR PD OR PK OR AD)/CT
L49        2280 SEA FILE=MEDLINE ABB=ON  GAUCHER DISEASE/CT
L52         170 SEA FILE=MEDLINE ABB=ON  L26/MAJ
L53         548 SEA FILE=MEDLINE ABB=ON  L49(L)TH./CT
L54         301 SEA FILE=MEDLINE ABB=ON  L53/MAJ
L55         144 SEA FILE=MEDLINE ABB=ON  L52 AND L54
L56          12 SEA FILE=MEDLINE ABB=ON  L55 AND REVIEW/DT
```

Subheadings
TU - therapeutic use
PD - pharmacology
PK - pharmacokinetics
AD - administration & dosage
TH - therapy

```
=> s l56 not l50
L102         12 L56 NOT L50
```

previously printed

```
=> fil embase; d que l85
FILE 'EMBASE' ENTERED AT 13:42:48 ON 15 OCT 2002
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 FILE COVERS 1974 TO 10 Oct 2002 (20021010/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L60         770 SEA FILE=EMBASE ABB=ON  GLUCOSYLCERAMIDASE/CT
L61        1923 SEA FILE=EMBASE ABB=ON  GAUCHER DISEASE/CT
L65         349 SEA FILE=EMBASE ABB=ON  L61(L)DT/CT
L76         108 SEA FILE=EMBASE ABB=ON  L60(L)(DT OR PK OR AD OR DO OR PD)/CT
L78         689 SEA FILE=EMBASE ABB=ON  ENZYME REPLACEMENT/CT
L84         501 SEA FILE=EMBASE ABB=ON  ENZYME THERAPY/CT
L85           9 SEA FILE=EMBASE ABB=ON  L65/MAJ AND L76/MAJ AND (L78 OR L84)
                AND GENERAL REVIEW/DT
```

Subheadings
DT - drug therapy
PK - pharmacokinetics
AD - administration
DO - dosage
PD - pharmacology

=> s l85 not (l71 or l66) previously printed
L103 9 L85 NOT (L71 OR L66)

=> fil wpids; d que l97; s l97 not l90
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L87 266 SEA FILE=WPIDS ABB=ON GAUCHER?
L91 94 SEA FILE=WPIDS ABB=ON GLUCOCEREBROSIDASE# OR GLUCOSYLCERAMIDASE# OR GLUCOSYL CERAMIDASE# OR CERAMIDE GLUCOSIDASE#
L92 2 SEA FILE=WPIDS ABB=ON GLUCOSE CEREBROSIDASE# OR GLUCOSYLCEREBROSIDASE# OR GLUCOXYL CEREBROSIDASE#
L96 5 SEA FILE=WPIDS ABB=ON (L91 OR L92)(5A)(ADMINIST? OR THERAP? OR REPLAC? OR EXOGENOUS?)
L97 4 SEA FILE=WPIDS ABB=ON L87 AND L96

L104 4 L97 NOT L90 previously printed

=> dup rem l102,l101,l103,l104
FILE 'MEDLINE' ENTERED AT 13:43:27 ON 15 OCT 2002

FILE 'CAPLUS' ENTERED AT 13:43:27 ON 15 OCT 2002
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PROCESSING COMPLETED FOR L102
PROCESSING COMPLETED FOR L101
PROCESSING COMPLETED FOR L103
PROCESSING COMPLETED FOR L104
L105 28 DUP REM L102 L101 L103 L104 (2 DUPLICATES REMOVED)
ANSWERS '1-12' FROM FILE MEDLINE
ANSWERS '13-16' FROM FILE CAPLUS
ANSWERS '17-24' FROM FILE EMBASE
ANSWERS '25-28' FROM FILE WPIDS

=> d ibib ab hitrn 1-28; fil hom

L105 ANSWER 1 OF 28 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 95057004 MEDLINE
DOCUMENT NUMBER: 95057004 PubMed ID: 7967500
TITLE: Modifying exogenous glucocerebrosidase for effective replacement therapy in Gaucher disease.
AUTHOR: Brady R O; Murray G J; Barton N W
CORPORATE SOURCE: Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD 20892.
SOURCE: JOURNAL OF INHERITED METABOLIC DISEASE, (1994) 17 (4) 510-9. Ref: 28
Journal code: 7910918. ISSN: 0141-8955.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 20000303
Entered Medline: 19941228

AB Important therapeutic principles were established in developing effective enzyme replacement therapy for patients with Gaucher disease. The background and sequence of the investigations that led to effective delivery of exogenous glucocerebrosidase to the lipid-storing macrophages in patients with Gaucher disease are described. The principle of targeting the intravenously injected enzyme to the mannose lectin on the surface of these cells by engineering the glycoform of the enzyme is a useful model of an essential requirement for effective enzyme therapy. Similar strategies are expected to be effective for the treatment of a number of hereditary metabolic disorders of humans.

L105 ANSWER 2 OF 28 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 92362554 MEDLINE
DOCUMENT NUMBER: 92362554 PubMed ID: 1379912
TITLE: Alglucerase. A review of its therapeutic use in Gaucher's disease.
AUTHOR: Whittington R; Goa K L
CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand.
SOURCE: DRUGS, (1992 Jul) 44 (1) 72-93. Ref: 84
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920925
Last Updated on STN: 20000303
Entered Medline: 19920917

AB Alglucerase is a mannose-terminated form of human placental glucocerebrosidase, developed to treat patients with Gaucher's disease. Functional glucocerebrosidase is deficient in Gaucher's disease, an autosomal recessive lipid storage disorder that affects people of all ethnic backgrounds, but has a higher incidence among East European Jews (Ashkenazim). Gaucher's disease manifests with hepatosplenomegaly, bleeding disorders and bone disease, with the more rare subtypes (types 2 and 3) featuring neurological dysfunction. Prior to the development of

enzyme replacement therapy, treatment for Gaucher's disease was mainly symptomatic relief. Primary treatment with glucocerebrosidase focuses on removal of the lipid metabolite that causes the pathology. Because of the rarity of Gaucher's disease clinical trials are small, and much of the data investigating alglucerase therapy have been obtained from studies of patients with type 1 disease, the prevalent subtype. Nonetheless, after intravenous administration of alglucerase, improvements are evident within 6 months of therapy. Patients have increased haemoglobin levels and platelet counts, and decreased incidences of epistaxis and bruising. Spleen and liver size are reduced, and skeletal parameters improve. Children gain height and most patients receiving alglucerase therapy are able to resume work and daily activities. Alglucerase is well tolerated, with few mild adverse reactions reported. Although the pharmacokinetic and pharmacodynamic information for alglucerase is limited, its unequivocal efficacy justifies enzyme replacement therapy with this compound as first-line treatment for patients with Gaucher's disease, for whom treatment options are limited.

L105 ANSWER 3 OF 28 MEDLINE
ACCESSION NUMBER: 2002030551 MEDLINE
DOCUMENT NUMBER: 21594229 PubMed ID: 11758685
TITLE: Clinically relevant therapeutic endpoints in type I Gaucher disease.
AUTHOR: Hollak C E; Maas M; Aerts J M
CORPORATE SOURCE: Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands.. c.e.hollak@amc.uva.nl
SOURCE: JOURNAL OF INHERITED METABOLIC DISEASE, (2001) 24 Suppl 2 97-105; discussion 87-8. Ref: 32
Journal code: 7910918. ISSN: 0141-8955.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20020425
Entered Medline: 20020424

AB The introduction of enzyme supplementation therapy for Gaucher disease has had a great impact on the lives of many patients. Organomegaly, cytopenia and bone disease have been shown to improve in response to treatment, resulting in an improvement in quality of life. However, the assessment of organ system involvement is not always done in such a way that the relationship with clinically relevant endpoints is clear. The lack of adequately validated methods of assessment, especially for bone disease, has hindered the establishment of treatment goals and guidelines for treatment optimization.

L105 ANSWER 4 OF 28 MEDLINE
ACCESSION NUMBER: 2002030550 MEDLINE
DOCUMENT NUMBER: 21594228 PubMed ID: 11758684
TITLE: Lessons learned from the development of enzyme therapy for Gaucher disease.
AUTHOR: Barranger J A; O'Rourke E
CORPORATE SOURCE: Department of Human Genetics, University of Pittsburgh, Pennsylvania 15261, USA.. jbarrang@helix.hgen.pitt.edu
SOURCE: JOURNAL OF INHERITED METABOLIC DISEASE, (2001) 24 Suppl 2 89-96; discussion 87-8. Ref: 89
Journal code: 7910918. ISSN: 0141-8955.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20020425
Entered Medline: 20020424

AB Enzyme replacement therapy for the lysosomal storage disorders derives its impetus from the successes achieved in the treatment of Gaucher disease. After nearly two decades of persistent but unsuccessful efforts, the promise of therapy through enzyme replacement was losing credibility. Then, the fortunate intersection of two different lines of scientific research produced the necessary breakthrough. The dramatic responses to enzyme replacement therapy in patients with Gaucher disease made it immediately clear that this treatment approach was a success. Furthermore, the large number of patients with the disorder guaranteed commercial involvement. The lessons learned from the development of enzyme replacement therapy for Gaucher disease are broadly applicable to other lysosomal storage diseases and will be reviewed in this paper.

L105 ANSWER 5 OF 28 MEDLINE
ACCESSION NUMBER: 1998320985 MEDLINE
DOCUMENT NUMBER: 98320985 PubMed ID: 9656829
TITLE: [Enzyme substitution in Gauscher disease]. Enzymsubstitution ved mb. Gaucher.
AUTHOR: Steensberg J; Nielsen K G; Brandt N J
CORPORATE SOURCE: H:S Rigshospitalet, Juliane Marie Centret, afsnit for klinisk genetik 4062.
SOURCE: UGESKRIFT FOR LAEGER, (1998 Jun 22) 160 (26) 3900-3. Ref: 21
Journal code: 0141730. ISSN: 0041-5782.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Danish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980811
Last Updated on STN: 20000303
Entered Medline: 19980728

AB Gaucher's disease is the most frequent inherited lysosomal storage disorder, displaying hepato-splenomegaly, thrombocytopenia, anaemia, and bone pain as characteristic features. Substitution with the modified enzyme alglucerase has revolutionized the treatment and prognosis of Gaucher's disease. Treatment in general and current trends in enzyme substitution therapy in particular are discussed.

L105 ANSWER 6 OF 28 MEDLINE
ACCESSION NUMBER: 1998326446 MEDLINE
DOCUMENT NUMBER: 98326446 PubMed ID: 9661800
TITLE: Enzyme therapy for Gaucher disease: the first 5 years.
AUTHOR: Grabowski G A; Leslie N; Wenstrup R
CORPORATE SOURCE: Division in Human Genetics, Children's Hospital Research Foundation, Cincinnati, OH 45229-3039, USA..
grabg0@chmcc.org
CONTRACT NUMBER: DK 36729 (NIDDK)
NS 34071 (NINDS)
NS 36681 (NINDS)
+
SOURCE: BLOOD REVIEWS, (1998 Jun) 12 (2) 115-33. Ref: 100
Journal code: 8708558. ISSN: 0268-960X.
PUB. COUNTRY: SCOTLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 20000303
Entered Medline: 19981007

AB Gaucher disease was first described by Philippe Gaucher in his 1882 medical thesis. Gaucher's original concept was of an unusual epithelioma of the spleen. By the early 1900s, Mandelbaum recognized the systemic nature of the disease. Several children with Gaucher disease were described at the turn of the century, but Rusca described a rapidly progressive fatal neurodegenerative type of disease, i.e. type 2, in the 1920s. The 'juvenile' form (type 3) of the disease was described in Sweden in the 1950s. In 1965, the deficient enzyme, acid beta-glucosidase, was discovered and the lysosomal nature of the disease was elucidated. Currently, three variants of Gaucher disease have been defined clinically and are distinguished by the presence and severity of neuronopathic involvement (Table 1). Each of these clinical types has substantial phenotypic variation, but types 1 and 3 have significantly heterogeneous rates of disease progression and degrees of visceral organs involvement. The neuronopathic involvement in type 3 also has substantial variation in the age of onset and disease progression even within relatively isolated communities. An extensive review of the clinical and pathologic involvement by Gaucher disease is available.

L105 ANSWER 7 OF 28 MEDLINE
ACCESSION NUMBER: 1998442152 MEDLINE
DOCUMENT NUMBER: 98442152 PubMed ID: 9770016
TITLE: [Gaucher's disease and enzyme replacement therapy]. Maladie de Gaucher et traitement par enzymotherapie substitutive.
AUTHOR: Cornu F
CORPORATE SOURCE: Genzyme SA, Cergy-Pontoise.
SOURCE: ANNALES PHARMACEUTIQUES FRANCAISES, (1998) 56 (3) 102-7. Ref: 17
Journal code: 2985176R. ISSN: 0003-4509.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20000303
Entered Medline: 19981105

AB Gaucher disease is an autosomal recessive genetic disorder characterized by a deficiency in the glucocerebrosidase enzyme. Glucocerebroside then accumulates in macrophages (Gaucher cells), causing anemia, thrombocytopenia, organomegaly and major bone problems. Discovery of the enzyme deficiency by Brady in 1964, and subsequent extraction and partial deglycosylation of the native enzyme led to a treatment. 1,600 people out of 5,000 possible worldwide patients benefit from this drug. The 70 French treated patients (out of an estimated 200) show remarkable improvement.

L105 ANSWER 8 OF 28 MEDLINE
ACCESSION NUMBER: 1998159297 MEDLINE
DOCUMENT NUMBER: 98159297 PubMed ID: 9497862
TITLE: Enzyme replacement therapy for Gaucher's disease.
AUTHOR: Beutler E

CORPORATE SOURCE: Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA 92037, USA.
CONTRACT NUMBER: RR00833 (NCRR)
SOURCE: BAILLIERES CLINICAL HAEMATOLOGY, (1997 Dec) 10 (4) 751-63. Ref: 43
Journal code: 8800474. ISSN: 0950-3536.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 20000303
Entered Medline: 19980317

AB Modified placental human glucocerebrosidase (alglucerase) and recombinant glucocerebrosidase (imiglucerase) are effective means of treating Type 1 Gaucher's disease. Amelioration of hepatosplenomegaly and of haematological manifestations is usually apparent within 6 months. Bone disease responds more slowly but within several years improvement is evident in most patients. Analysis of a large body of data demonstrates that the rate of response of all manifestations of Gaucher's disease is independent of dose over the range of 30 to 260 U/kg body weight per month. Even the response to 15 U/kg per month appears to be equivalent under most circumstances; treatment failures are the same in patients treated with 15, 30 and 130 U/kg per month. Patients with severe manifestations respond more rapidly than those with mild disease, and this, too, is true at all but the 15 U/kg per month dosage level. All available data thus support the administration of no more than 15 to 30 U of alglucerase or imiglucerase per kg/month. Frequent dosing, i.e. three times weekly, appears to be the most effective means of administration.

L105 ANSWER 9 OF 28 MEDLINE
ACCESSION NUMBER: 96242832 MEDLINE
DOCUMENT NUMBER: 96242832 PubMed ID: 8684492
TITLE: [The treatment of Gaucher's disease in The Netherlands using enzyme substitution therapy].
Behandeling van de ziekte van Gaucher in Nederland met enzymvervangingstherapie.
AUTHOR: Hollak C E; van Oers M H; Maaswinkel P; Aerts J M; Goudsmit R
CORPORATE SOURCE: Universiteit van Amsterdam, Academisch Medisch Centrum, Afd. Inwendige Geneeskunde en Hematologie.
SOURCE: NEDERLANDS TIJDSCHRIFT VOOR GENEESKUNDE, (1996 May 11) 140 (19) 1011-3. Ref: 17
Journal code: 0400770. ISSN: 0028-2162.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Dutch
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960828
Last Updated on STN: 20000303
Entered Medline: 19960822

L105 ANSWER 10 OF 28 MEDLINE
ACCESSION NUMBER: 97014993 MEDLINE
DOCUMENT NUMBER: 97014993 PubMed ID: 8861826

TITLE: Alglucerase (Ceredase).
AUTHOR: Wiltink E H; Hollak C E
CORPORATE SOURCE: Department of Clinical Pharmacy, St. Antonius Hospital, Koekoekslaan 1, Nieuwegein, The Netherlands.
SOURCE: PHARMACY WORLD AND SCIENCE, (1996 Jan) 18 (1) 16-9. Ref: 12
Journal code: 9307352. ISSN: 0928-1231.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 20000303
Entered Medline: 19970206

L105 ANSWER 11 OF 28 MEDLINE
ACCESSION NUMBER: 96047864 MEDLINE
DOCUMENT NUMBER: 96047864 PubMed ID: 10155294
TITLE: Alglucerase. A pharmacoeconomic appraisal of its use in the treatment of Gaucher's disease.
COMMENT: Comment in: Pharmacoeconomics. 1995 Jul;8(1):82-3
AUTHOR: Whittington R; Goa K L
CORPORATE SOURCE: Adis International limited, Auckland, New Zealand.
SOURCE: PHARMACOECONOMICS, (1995 Jan) 7 (1) 63-90. Ref: 100
Journal code: 9212404. ISSN: 1170-7690.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Health Technology
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 20010223
Last Updated on STN: 20010223
Entered Medline: 19951114

AB Alglucerase is a modified form of human placental glucocerebrosidase used as enzyme replacement therapy for patients with Gaucher's disease, in whom functional glucocerebrosidase is deficient. Alglucerase has provided a breakthrough in treatment for patients with this relatively rare disease. With alglucerase infusions typical disease manifestations are ameliorated or normalised: hepatosplenomegaly is reduced, haematological parameters improve, and patients experience an increased quality of life usually within 4 to 6 months of treatment. Parameters of bone disease also respond, but generally over a longer period of treatment. Alglucerase is well tolerated by children and adults, with few adverse effects reported. Seroconversion occurs in approximately 15% of patients on high-dose therapy, but does not appear to affect the efficacy of treatment. Several dosage regimens have been used to deliver alglucerase, and the comparative benefits of these remain controversial. High-dose regimens of 60 IU/kg bodyweight administered every 2 weeks are clearly effective; however, smaller dosages given more frequently are also effective and incur a greatly reduced acquisition cost. Patient responses are variable, and the dosage regimen should be tailored to individual needs. Dosage regimens may be considerably reduced for the maintenance phase of treatment, but clinical experience is as yet insufficient to establish the minimum dosages required in the long term. Acquisition cost of alglucerase is $US3.70 per unit (1994 US dollars); thus, a dosage regimen of 60 IU/kg bodyweight administered every 2 weeks for a patient weighing 70kg costs $US404,040 per year. The minimal costs per quality-adjusted life year saved (QALY) have been estimated for 3 dosage regimens over a 10-year

period. Cost per QALY was $US147,000 for 60 IU/kg bodyweight administered every 2 weeks, $US75,000 for 30 IU/kg every 2 weeks, and $US49,000 for 2.3 IU/kg administered 3 times per week. These costs were calculated assuming immediate death with no treatment, which suggests that the actual costs per QALY for most patients with type 1 or 3 disease are likely to be much higher. Drug administration costs may become a significant part of the cost during maintenance therapy; in addition, possible cost savings due to increased patient productivity and reduced palliative treatments remain unresolved. Although some patients may obtain increased benefit from high-dosage regimens, the very high cost may preclude general use of these regimens. Healthcare resources consumed by alglucerase therapy represent a large opportunity cost for other therapeutic areas.(ABSTRACT TRUNCATED AT 400 WORDS)

L105 ANSWER 12 OF 28 MEDLINE
ACCESSION NUMBER: 93248920 MEDLINE
DOCUMENT NUMBER: 93248920 PubMed ID: 8097903
TITLE: Gaucher disease: a heterogeneous clinical complex for which effective enzyme replacement has come of age.
AUTHOR: Frenkel E P
CORPORATE SOURCE: Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas 75235-8852.
SOURCE: AMERICAN JOURNAL OF THE MEDICAL SCIENCES, (1993 May) 305 (5) 331-44. Ref: 92
Journal code: 0370506. ISSN: 0002-9629.
PUB. COUNTRY: United States
DOCUMENT TYPE: Conference; Conference Article; (CONGRESSES)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 20000303
Entered Medline: 19930602

AB Gaucher disease, the most common form of lysosomal storage disease, is the result of autosomal recessive inheritance of a lysosomal enzyme glucocerebrosidase deficiency, which produces defective hydrolysis of glucosylceramide that accumulates in reticuloendothelial (tissue macrophage) cells. The current review focuses on Type 1 (the nonneuronopathic) or adult Gaucher disease and defines the clinical manifestations (splenomegaly, hepatomegaly, bony lesions, and clinical metabolic dysfunction) in relationship to the known enzymatic defect. The clinical diversity and variability in symptoms and signs, the age at onset of the clinical manifestations and their rate of progression, and the heterogeneity of the organs involved are reviewed. Extensive delineation of the nature of the enzyme defect and the recent molecular characterization of the enzyme mutants has not provided an explantation for the remarkable clinical phenotypic heterogeneity. Enzyme assays now provide an excellent method for diagnosis. Effective enzyme replacement therapy emphasizes the value of early diagnosis and has altered the costs and potential risks of older therapeutic indications for splenectomy or cytokine therapy. Enzyme efficacy raises questions about the specific indications for replacement treatment and the most desirable rate and duration of enzyme delivery.

L105 ANSWER 13 OF 28 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:208390 CAPLUS
DOCUMENT NUMBER: 134:248843
TITLE: Use of GlcNAc-phosphotransferase and phosphodiester .alpha.-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases

Searched by Barb O'Bryen, STIC 308-4291

INVENTOR(S): Canfield, William M.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019955	A2	20010322	WO 2000-US21970	20000914
WO 2001019955	A3	20011004		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000073303	A5	20010417	AU 2000-73303	20000914
BR 2000014514	A	20020723	BR 2000-14514	20000914
EP 1224266	A2	20020724	EP 2000-961335	20000914
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 2002025550	A1	20020228	US 2001-895072	20010702

PRIORITY APPLN. INFO.:
US 1999-153831P P 19990914
US 2000-635872 A1 20000810
WO 2000-US21970 W 20000914

AB The lysosomal targeting pathway enzymes GlcNAc-phosphotransferase and phosphodiester .alpha.-GlcNAcase and uses in prodn. of highly phosphorylated lysosomal hydrolases that can be used to treat lysosomal storage diseases, are disclosed. Generally, the nucleic acid mols. coding for the enzymes are incorporated into expression vectors that are used to transfect host cells that express the enzymes. The expressed enzymes are recovered using monoclonal antibodies capable of selectively binding to bovine GlcNAc-phosphotransferase and to bovine phosphodiester .alpha.-GlcNAcase. Lysosomal hydrolases having high mannose structures are treated with GlcNAc-phosphotransferase and phosphodiester .alpha.-GlcNAcase resulting in the prodn. of asparagine-linked oligosaccharides that are highly modified with mannose 6-phosphate ("M6P"). The treated hydrolase binds to M6P receptors on the cell membrane and is transported into the cell and delivered to the lysosome where it can perform its normal or a desired function. The highly phosphorylated lysosomal hydrolases are readily taken into the cell and into the lysosome during enzyme replacement therapy procedures.

IT **37228-64-1**, Glucocerebroside .beta.-Glucosidase
RL: BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(use of GlcNAc-phosphotransferase and phosphodiester .alpha.-GlcNAcase in prodn. of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

IT **155501-85-2**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(use of GlcNAc-phosphotransferase and phosphodiester .alpha.-GlcNAcase in prodn. of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

L105 ANSWER 14 OF 28 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:795028 CAPLUS
DOCUMENT NUMBER: 128:97211
TITLE: Gene therapy for Gaucher disease via genetically engineered primary myoblasts
AUTHOR(S): Liu, Chunming; Watkins, Simon; Bahnson, Alfred; Barranger, John A.
CORPORATE SOURCE: Germany
SOURCE: Concepts in Gene Therapy (1997), 283-295. Editor(s): Strauss, Michael; Barranger, John A. de Gruyter: Berlin, Germany.
CODEN: 65LFAB
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review with 40 refs.
IT **37228-64-1**, Glucocerebrosidase
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(gene therapy for **Gaucher** disease via genetically engineered primary myoblasts)

L105 ANSWER 15 OF 28 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:60923 CAPLUS
DOCUMENT NUMBER: 128:188137
TITLE: Macrophage-targeted glucocerebrosidase: a therapeutically effective enzyme replacement product for Gaucher disease
AUTHOR(S): Barton, Norman W.; Brady, Roscoe O.
CORPORATE SOURCE: Biotechnology General Corporation, Iselin, NJ, USA
SOURCE: Drugs and the Pharmaceutical Sciences (1997), 84(Pharmaceutical Enzymes), 261-283
CODEN: DPHSDS; ISSN: 0360-2583
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 50 refs. Several important principles were established in the course of developing effective enzyme replacement therapy for Gaucher disease. Nascent investigations, carbohydrate modification of glucocerebrosidase, first demonstration of clin. responses to macrophage-targeted glucocerebrosidase, dose-response trial, clin. efficacy trial, how broad is the clin. effective dosage range, and addnl. projects and future investigations are discussed. It was anticipated that the lessons learned during these investigations will be applicable in the design of treatments for other heritable storage disorders.
IT **37228-64-1**, .beta.-Glucocerebrosidase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(macrophage-targeted glucocerebrosidase as enzyme replacement product for **Gaucher** disease)

L105 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:437773 CAPLUS
DOCUMENT NUMBER: 127:120028
TITLE: Gaucher disease
AUTHOR(S): Eto, Yoshikatsu
CORPORATE SOURCE: Dep. Pediatrics, Tokyo Jikei Univ. Med. Sch., Japan
SOURCE: Lipid (1997), 8(3), 235-240
CODEN: LIPDET; ISSN: 0915-6607
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review, with 6 refs., discussing characteristics of gene mutations in Gaucher disease in human. A discussion of the transfer and sustained high expression of the human glucocerebrosidase gene in mice and their

functional macrophages following transplantation of the bone marrow transduced by a retroviral vector is also presented.

IT **37228-64-1**, Glucocerebrosidase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(gene mutations and transfer in human **Gaucher** disease)

L105 ANSWER 17 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998370386 EMBASE
TITLE: [Low dose enzyme replacement therapy in paediatric type 1 Gaucher's disease].
TERAPIA ENZIMATICA SOSTITUTIVA A BASSE DOSI NELLE FORME PEDIATRICHE DI MALATTIA DI GAUCHER TIPO 1.
AUTHOR: Bembi B.; Donda M.G.; Martini C.; Zanatta M.; Boscolo R.; Katouzian F.; Ciana G.
CORPORATE SOURCE: B. Bembi, Ctro. Diagn. e cura Malattia Gaucher, Malattie Congenite del Metabolismo, Ist Ric. Cura Carat. Sci B. Garofolo, via dell'Istria 65/1, 34137 Trieste, Italy
SOURCE: Rivista Italiana di Pediatria, (1998) 24/1 (93-98).
Refs: 31
ISSN: 0392-5161 CODEN: RITODB
COUNTRY: Italy
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
LANGUAGE: Italian

L105 ANSWER 18 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998014554 EMBASE
TITLE: A practical approach to diagnosis and management of Gaucher's disease.
AUTHOR: Mistry P.K.; Abrahamov A.
CORPORATE SOURCE: P.K. Mistry, Hepato-biliary Liver Transplant Unit, Royal Free Hospital, School of Medicine, Pond Street, London NW3 2QG, United Kingdom
SOURCE: Bailliere's Clinical Haematology, (1997) 10/4 (817-838).
Refs: 86
ISSN: 0950-3536 CODEN: BCHAEW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 012 Ophthalmology
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The diagnosis of Gaucher's disease is established by demonstration of reduced acid .beta.-glucosidase activity in peripheral blood leukocytes. Genotyping at the glucocerebrosidase gene locus can give additional prognostic information and facilitate carrier detection. However, extreme phenotypic diversity precludes reliable prediction of prognosis in individual patients. Histological diagnosis of Gaucher's disease is unnecessary and can be misleading. A range of clinical, radiological and laboratory parameters are useful for staging disease activity which is central to achieving optimal timing to initiate enzyme therapy. Treatment should be individualized to obtain maximum therapeutic response. The recent introduction of chitotriosidase measurements has provided a valuable indicator of total cellular burden of storage cells. Serial measurements of chitotriosidase activity are useful for monitoring disease progression as well as response to therapy. A number of adjuvant therapies are available for use in conjunction with enzyme treatment. Special

considerations apply to management of affected children.

L105 ANSWER 19 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94213382 EMBASE
DOCUMENT NUMBER: 1994213382
TITLE: Enzyme replacement therapy for Gaucher disease: Critical investigations beyond demonstration of clinical efficacy.
AUTHOR: Brady R.O.; Barton N.W.
CORPORATE SOURCE: Devtl./Metabolic Neurology Branch, NINDS, National Institutes of Health,Bethesda, MD 20892, United States
SOURCE: Biochemical Medicine and Metabolic Biology, (1994) 52/1 (1-9).
ISSN: 0885-4505 CODEN: BMMBES
COUNTRY: United States
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
022 Human Genetics
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Enzyme replacement therapy is highly effective for patients with Type 1 Gaucher disease. In order to estimate the quantity of enzyme that would be necessary for clinical benefit, we conducted a single-infusion, dose-response study in nonsplenectomized patients with Gaucher disease. Biochemical and histologic changes were compared in liver biopsy specimens obtained before and 44 h following the infusion of varying quantities of enzyme. Based on the information obtained from this investigation, patients in our initial clinical efficacy trial were given 60 IU of macrophage-targeted glucocerebrosidase/kg body wt every other week. All patients had significant improvement of their anemia and reduction of splenomegaly after 6 months of treatment. In a subsequent investigation, 10 moderately symptomatic patients with intact spleens were given 10 IU of glucocerebrosidase/kg body wt every other week. After 6 months of treatment, only a portion of these patients had beneficial responses. We concluded that the rate and extent of response to enzyme replacement therapy in patients with Gaucher disease are dependent upon the quantity of enzyme administered. When treatment is initiated in patients with mild to moderately severe disease, a lower dose of enzyme can be selected. Moreover, the maintenance dose of glucocerebrosidase has been shown to be much less than the amount initially required to reduce the accumulated lipid. Some patients require enzyme infusions on only a monthly basis, and it is possible that even this frequency may eventually be reduced. These refinements in treatment strategy merit serious consideration for the long-term management of patients with Gaucher disease.

L105 ANSWER 20 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93159507 EMBASE
DOCUMENT NUMBER: 1993159507
TITLE: Clinical and therapeutic perspectives on Gaucher disease.
AUTHOR: Grabowski G.A.
CORPORATE SOURCE: Division of Human Genetics, Children's Hospital Medical Center, Elland and Bethesda Avenues,Cincinnati, OH 45229-2899, United States
SOURCE: International Pediatrics, (1993) 8/1 (22-29).
ISSN: 0885-6265 CODEN: INPDEV
COUNTRY: United States
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Gaucher disease is the most frequent lysosomal storage disease. Strong genotype/phenotype correlations have been found between common mutations at the acid .beta.-glucosidase locus and the types and severity of Gaucher disease. Enzyme replacement therapy has demonstrated efficacy at several different dosages and provides for reversal of disease manifestations in even the most severely affected nonneuronopathic patients. The high frequency of this disease, the genotype/phenotype correlations and the availability of therapy makes Gaucher disease a prototype for developing broadened approaches to screening and intervention programs which will be applicable to other inborn errors of metabolism.

L105 ANSWER 21 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92349216 EMBASE
DOCUMENT NUMBER: 1992349216
TITLE: Creating the costliest orphan: The Orphan Drug Act in the development of Ceredase(TM).
AUTHOR: Goldman D.P.; Clarke A.E.; Garber A.M.
CORPORATE SOURCE: National Economic Res. Bureau, Inc., 204 Junipero Serra Boulevard,Stanford, CA 94305-8091, United States
SOURCE: International Journal of Technology Assessment in Health Care, (1992) 8/4 (583-597).
ISSN: 0266-4623 CODEN: IJTCEK
COUNTRY: United States
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 006 Internal Medicine
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The FDA recently approved Ceredase(TM), a new treatment for Gaucher's disease, under the provisions of the Orphan Drug Act. Ceredase(TM) is unusually expensive, but there are no satisfactory alternative therapies. It appears likely that Ceredase(TM) would not have become available without the protection of the Orphan Drug Act, but its expense and the lack of information about its long-term effects on health raise questions about whether the ODA provides appropriate incentives to develop cost-effective technologies.

L105 ANSWER 22 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92213811 EMBASE
DOCUMENT NUMBER: 1992213811
TITLE: Pediatrics.
AUTHOR: Barness L.A.
CORPORATE SOURCE: University of Wisconsin,Madison, WI, United States
SOURCE: Journal of the American Medical Association, (1992) 268/3 (399-401).
ISSN: 0098-7484 CODEN: JAMAAP
COUNTRY: United States
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English

L105 ANSWER 23 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92213803 EMBASE
DOCUMENT NUMBER: 1992213803
TITLE: Neurology.
AUTHOR: Joynt R.J.
CORPORATE SOURCE: University of Rochester, School of Medicine and Dentistry,Rochester, NY, United States
SOURCE: Journal of the American Medical Association, (1992) 268/3 (380-382).

ISSN: 0098-7484 CODEN: JAMAAP
COUNTRY: United States
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L105 ANSWER 24 OF 28 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91339810 EMBASE
DOCUMENT NUMBER: 1991339810
TITLE: Current concepts: Gaucher's disease.
AUTHOR: Beutler E.
CORPORATE SOURCE: Dept. of Molecular/Exptl. Med., Scripps Research Institute, 10666 N. Torrey Pines Rd.,La Jolla, CA 92037, United States
SOURCE: New England Journal of Medicine, (1991) 325/19 (1354-1360).
ISSN: 0028-4793 CODEN: NEJMAG
COUNTRY: United States
DOCUMENT TYPE: Journal; **General Review**
FILE SEGMENT: 006 Internal Medicine
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L105 ANSWER 25 OF 28 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-329381 [36] WPIDS
DOC. NO. CPI: C2002-095089
TITLE: Polymer based intracellular delivery system useful for delivery of polypeptides for antitumor, antiinflammatory or immunosuppressive therapy, and for treatment of genetic and **Gaucher**'s disease.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): LAVI, S; SATCHI-FAINARO, R
PATENT ASSIGNEE(S): (UYRA-N) UNIV RAMOT APPLIED RES & IND DEV LTD
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002007671	A2	20020131	(200236)*	EN	73

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001080035 A 20020205 (200236)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002007671	A2	WO 2001-IL689	20010726
AU 2001080035	A	AU 2001-80035	20010726

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001080035	A	Based on	WO 200207671

PRIORITY APPLN. INFO: US 2000-668713 20000922; US 2000-220971P

20000726

AB WO 200207671 A UPAB: 20020610

NOVELTY - A complex molecule (I), comprising a conjugate of a polymer capable of being taken up by a cell linked to a biologically active polypeptide, is new. The conjugate is capable of achieving intracellular delivery of the polypeptide while retaining its biological activity. The biologically active peptide is other than an antibody which binds to a cell surface marker or receptor.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition comprising (I) as an active ingredient; and

(2) a method which comprises contacting an eukaryotic cell with a composition comprising a carrier and a polymer capable of being taken up by a cell, the polymer being linked to a polypeptide, which enters the cell and exhibits an enzymatic activity within the cell.

ACTIVITY - Immunosuppressive; Cytostatic; Antiinflammatory; Vasotropic.

Antitumor activity of hydroxypropyl methacrylamide (HPMA) copolymer-protein phosphatase 2C (PP2C) conjugate was evaluated. Male C57BL/6J mice were inoculated with 105 viable B16F10 melanoma cells subcutaneously. The tumor was allowed to establish until the area was 20-50 mm2 as measured by the product of two orthogonal diameters. Animals were injected intravenously by the tail vein in a single treatment with HPMA-PP2C conjugate (20 mg/kg polypeptide equivalent in saline). Additional groups of animals were treated with saline (100 micro l intravenously) as control. Each group consisted of 6 mice. Animals were weighed and the tumor measured daily. Animals were monitored for general health, weight loss and tumor progression. There was no weight loss. Mice were culled when the tumor reached or surpassed the size of 300 mm2. At termination, the animals were examined and the tumors were dissected and weighed. The results showed that the growth of the tumor was much slower in the mice treated with the conjugate. The conjugate caused complete regression of the tumor, without the fear of immunogenicity.

MECHANISM OF ACTION - Delivers polypeptides into cells.

USE - (I) is useful for intracellular delivery of a polypeptide such as a **therapeutic** antibody, intrabody, toxin, enzyme (**glucocerebrosidase**), anti-tumor polypeptide, antiinflammatory polypeptide or a polypeptide for immunosuppressive therapy used in transplantation procedure, and a polypeptide for treatment of genetic disease, autoimmune disease, or a polypeptide for preventing re-occlusion or restenosis. (I) is useful for treating a subject suffering from a disorder or a symptom in a subject, and in the preparation of a medicament for treating genetic disease or **Gaucher**'s disease. (All claimed). (I) is useful for therapeutic and diagnostic purposes and delivers polypeptides for which the cells that are the target have no receptors. (I) is useful in delivery of polypeptide for therapy of any condition which requires intracellular delivery of polypeptide, and for elucidation of the activity of unknown proteins and polypeptides. (I) is useful for transplantation procedure, more preferably for corneal transplantation.

ADVANTAGE - (I) delivers the polypeptide to the correct compartment of the cell and after intracellular delivery, the polypeptides are not immediately degraded, but retain biological activity.

Dwg.0/16

L105 ANSWER 26 OF 28 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-529882 [58] WPIDS
CROSS REFERENCE: 2001-522553 [57]
DOC. NO. CPI: C2001-158064
TITLE: Treating a patient with a lysosomal storage disease comprises administering a bisphosphonate compound to induce apoptosis of macrophages.

DERWENT CLASS: B04 D16
INVENTOR(S): CHENG, S; GOLDBERG, M; MARSHALL, J; ZIEGLER, R
PATENT ASSIGNEE(S): (CHEN-I) CHENG S; (GOLD-I) GOLDBERG M; (MARS-I) MARSHALL J; (ZIEG-I) ZIEGLER R; (GENZ) GENZYME CORP
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001060377 A2		20010823	(200158)*	EN	25
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR					
W: AU CA JP					
US 2001031741 A1		20011018	(200166)		
AU 2001036713 A		20010827	(200176)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001060377 A2		WO 2001-US3875	20010206
US 2001031741 A1	Provisional	US 2000-183296P	20000217
	Provisional	US 2001-260069P	20010105
		US 2001-777743	20010206
AU 2001036713 A		AU 2001-36713	20010206

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2001031741 A1		20 011110 WO 200160414
AU 2001036713 A	Based on	WO 200160377

PRIORITY APPLN. INFO: US 2001-260069P 20010105; US 2000-183296P 20000217; US 2001-777743 20010206

AB WO 200160377 A UPAB: 20011010
NOVELTY - Treating (M1) a patient suffering from an accumulation of a metabolite within macrophages comprising treating the patient with a macrophage depleting amount of bisphosphonate compound (I) to induce apoptosis of macrophages to release the metabolite into circulation so that it may be eliminated from the patient, is new.

ACTIVITY - Osteopathic; hepatotropic; nootropic; neuroprotective; analgesic.

MECHANISM OF ACTION - Apoptosis-inducer; gene-therapy.

1 x 109 particles of adenovirus encoding alpha galactosidase A (AD2/CMVHI alpha gal) were injected into the tail vein of two groups of Fabry mice. One group had been pre-treated with clodronate liposomes. Organs were divided to be assayed alpha-galactosidase A expression and GL-3 levels. Tissues were assayed by ELISA. Clodronate liposome pre-treatment enhanced levels and persistence of expression from 1 X 109 particles of AD2/CMVHI alpha gal with resulting GL-3 clearance in all tissues except kidney. The dose of vector was not sufficient to clear GL-3 in Fabry mice treated with virus alone.

USE - The method is useful for treating a patient suffering from an accumulation of a metabolite within macrophages especially patients with lysosomal storage diseases such as Pompe disease, Hurler's disease, Niemann-pick disease, Fabry's disease and **Gaucher**'s disease (all claimed).

ADVANTAGE - The gene therapy treatment allows persistent expression of therapeutic levels of lysosomal storage enzymes produced from gene therapy vectors and at lower dosage regimens than conventional treatments. The treatment with (I) eliminates significant amounts of lysosomal storage products which are usually sequestered within macrophages.
Dwg.0/6

L105 ANSWER 27 OF 28 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1998-099801 [09] WPIDS
CROSS REFERENCE: 1994-217531 [26]; 1997-243960 [21]
DOC. NO. CPI: C1998-032886
TITLE: Treating **Gaucher**'s disease by **administering** a **glucocerebrosidase** conjugate - which includes recombinant glucocerebrosidase to which poly(alkylene oxide) strands are linked via a urethane linkage.
DERWENT CLASS: A25 A96 B04 D16
INVENTOR(S): CHO, M; GILBERT, C W; GINNS, E J; MARTIN, B M; SHORR, R G L
PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICES
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5705153	A	19980106	(199809)*		5

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5705153	A	CIP of	US 1992-989802	19921210
		Div ex	US 1994-346680	19941130
			US 1996-735961	19961023

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5705153	A	Div ex	US 5620884

PRIORITY APPLN. INFO: US 1994-346680 19941130; US 1992-989802 19921210; US 1996-735961 19961023
AB US 5705153 A UPAB: 19980302
Treatment of **Gaucher**'s disease comprises **administration** of a **glucocerebrosidase** (GC) conjugate which has enhanced enzymatic activity at pH ranges 4.0-5.0 and 6.5-7.5, and which comprises recombinant GC and 1-25 poly(alkylene oxide) strands, each of which has a molecular weight of 1,000-15,000 and is covalently linked, via a urethane linkage, to an amino group on the recombinant GC.
USE - **Gaucher**'s disease is an autosomal recessive genetic disorder. It is the most common lysosomal storage disorder and is related to a defect in naturally occurring GC. There is currently no cure.
ADVANTAGE - The conjugates are resistant to in vivo hydrolysis, and thus require less frequent administration when compared to unmodified enzyme preparations. They exhibit prolonged activity against accumulated glycolipids.
Dwg.0/0

L105 ANSWER 28 OF 28 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1993-274677 [35] WPIDS
DOC. NO. CPI: C1993-122479
TITLE: Detection of **Gaucher**'s disease - by screening DNA for a substitution of adenine for guanine at position 1 of gluco cerebrosidase gene intron 2.
DERWENT CLASS: B04 D16
INVENTOR(S): BEUTLER, E
PATENT ASSIGNEE(S): (SCRI) SCRIPPS RES INST
COUNTRY COUNT: 21

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 558257	A1	19930901	(199335)*	EN	42
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
CA 2089351	A	19930825	(199346)		
US 5266459	A	19931130	(199349)		27
JP 06098798	A	19940412	(199419)		30
JP 2502024	B2	19960529	(199626)		30
KR 9510188	B1	19950911	(199846)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 558257	A1	EP 1993-301301	19930223
CA 2089351	A	CA 1993-2089351	19930211
US 5266459	A	US 1992-841652	19920224
JP 06098798	A	JP 1993-58076	19930224
JP 2502024	B2	JP 1993-58076	19930224
KR 9510188	B1	KR 1993-2489	19930224

FILING DETAILS:

PATENT NO	KIND		PATENT NO
JP 2502024	B2	Previous Publ.	JP 06098798

PRIORITY APPLN. INFO: US 1992-841652 19920224

AB EP 558257 A UPAB: 19970502

Human genetic screening method comprises assaying a nucleic acid sample isolated from a human for the presence of a glucocerobrosidae (GC) gene point mutation characterised as a substn. of an adenine nucleotide for a guanine nucleotide at nucleotide postion 1 of GC gene intron 2.

The method may further comprise assaying for the presence of (i) a GC gene insertion mutation characterised as an insertion of a guanine nucleotide adjacent to nucleotide position 57 of GC gene exon 2, (ii) a GC gene point mutation characterised as a change from an adenine nucleotide to a guanine nucleotide at nucleotide position 2 of GC gene exon 9, or (iii) a GC gene point mutation characterised as a change from a thymine nucleotide to a cytosine nucleotide at nucleotide position 60 of GC gene exon 10.

USE - The methods are used for screening humans for GC alleles associated with **Gaucher**'s disease. They can be used to diagnose either the disease itself or a heterozygous carrier state.

Dwg.0/0

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